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## ON SOME UNPUBLISHED LETTERS OF LAENNEC*

By W. S. Thayer

One hundred years ago, on or about the 15th of August, 1819, there appeared a book which marked the beginning of an epoch in medical history. One hundred years ago to-day the author was a tired, ill man, seeking a little rest and recreation in his beloved Kerlouarnec near Douarnenez on the coast of Brittany, endeavouring to stay the inroads of a disease which had carried away already his friends Bichat and Bayle, that malady to which he had devoted such brilliant and fertile studies only to fall in the end its victim.

The last two years have brought to me several opportunities to visit some of the scenes of Laennec's boyhood, and through the great kindness of his biographer, Professor Rouxeau and Dr. Cornillot, librarian of the *Bibliothèque de l'Ecole de médecine* in Paris, I have had the opportunity to examine the relics preserved at the museum of the *Ecole de médecine* at Nantes, and to study some of his precious manuscripts.

A few days before my return from Paris last September it was my good fortune to come into possession of the three letters which I take pleasure in showing you.

A word to begin with on the circumstances of his life. René Théophile Hyacinthe Laennec was born at Quimper, in Brittany, on the 17th of February, 1781. 'Tis a charming little town, Quimper, situated at the junction of the rivers Steir and Odet. The town, flanked by a high hill, lies along the banks of the Odet with its rushing tide. The house in which Laennec was born stood on the quay itself. His father, Théophile Marie Laennec, was a notary, a native of Quimper. His mother was an Angevine of noble extraction. The name,[1] Celtic in origin, comes probably from the word "*Lenn*" which signifies study or reading; it might properly be translated "reader" or "man of study." It is pronounced as if it were spelled "Lennec"; that is, it *should* so be pronounced. Oddly enough, even in France, it is commonly mispronounced "Laënnec." This is wrong, the diæresis having been added only in recent years by one of his biographers, Théophile Ambroise. None of his family use the diæresis in the spelling of their name, and his collateral descendants pronounce their name "Lennec."

*Read before The Johns Hopkins Hospital Medical Society on March 29, 1920.

[1] Saintignon, Dr. Henri: Laennec: Sa vie et son œuvre, 12°. Paris, J. B. Baillière et fils, 1904.

Five years after his birth his mother died, probably of tuberculosis, and Théophile and his younger brother "Michaud" were placed under the care of their uncle, the Curé of Elliant. On the removal of the uncle two years later, the two boys were sent to Nantes, where they were put under the care of another uncle, Dr. Guillaume François Laennec, who, at this time, was rector of the local university.

Laennec's early education was gained at the *Institut Tardivel* and the *Collège de l'oratoire*, which in the school year '91-'92, when Théophile entered, was under the direction of no less a personage than the celebrated Fouché, then a priest. In his uncle William, who was a physician of no mean ability, who had studied with John Hunter in London, Laennec found a devoted friend and adviser, a father indeed, far more of a father than his own brilliant but vain and scatter-brained parent. Some of the talents and tendencies of this parent he inherited and manifested early in his career, to the considerable discomfiture of his uncle; such for instance as a remarkable facility in versification.

In 1795 he began to study medicine at the Hôtel-Dieu de Nantes. At the same time he was an ardent student of the classics. At the age of 11 he translated the first eclogue of Virgil into excellent French verse. He was especially interested in Greek. While devoted to out-door sports and to natural history, the boy, rather early, became impressed with the desirability of perfecting himself in a variety of arts and graces which might fit him better to commune with the great world. He desired earnestly to take lessons in dancing. He felt that he should learn how to play some musical instrument and, indeed, became a flute player. He could not help playing the flute. No one with an upper lip like his could fail to play the flute.

In 1798 a severe continued fever, probably typhoid, nearly cut short his career.

In 1800 he accompanied the forces of General Grigny as an army surgeon during the campaign in le Morbihan, passing his time principally at Vannes and Redon. During this campaign he wrote an amusing poem entitled "La guerre des Venêtes" which purported to be a translation of the work of an old Celtic bard, Cardoe, by a Breton of the name of "Cenneal"—obviously his own name reversed. The manuscript of this interesting production which his father had, or sought to have done into Celtic, was lost for a number of years. It has recently been found and is now in the possession of Professor Rouxeau.

For several years it looked as if the improvident parent might fail to produce the wherewithal to send his brilliant son to Paris, but finally, in 1801 Laennec entered the *Collège spécial de santé*. There he devoted himself especially to study in the clinic of Corvisart at the *Charité*, then known as the *Unité*. He became a companion of the brilliant Bayle, with whom he began important anatomical and pathological studies under Dupuytren. This early anatomical work, normal and pathological, was notable. He was the first to describe the subdeltoid bursa, as well as the fibrous capsule of the liver. At the age of 21, in a remarkable communication, the result of the analysis of six cases with necropsies, he set forth the first clear clinical and anatomical picture of peritonitis. For general peritonitis Laennec did that which, some 80 odd years later, Fitz did for appendicitis.

At the same time his brother Michaud, who was preparing for the law, was gaining new laurels. In 1802 this brilliant boy entered three contests at the *Ecole des quatre nations*, taking the first prize in all—French, Latin literature and general grammar. In the following year Théophile, in the *Concours des Ecoles spéciales de Paris*, took the first prize in medicine and surgery. He was bitterly disappointed in missing like honours in chemistry and anatomy. The reputation of the brothers had, however, become so formidable that when at the next concours of the *Ecole pratique*, his name was entered, there were no contestants, and at the request of his instructors, he withdrew from the contest.

In 1804 Laennec published a remarkable article on "*Vers résiculaires*." Some of his original drawings for this publication I saw last summer at Nantes. He cannot be said to have been an artist, but the work was carefully and well done.

In the same year he published his thesis, "*Propositions sur la doctrine d'Hippocrate rélativement à la médecine.*" The thesis contains much that is interesting and sound. Here is a paragraph:

> **The only method by which one can acquire solid knowledge in medicine depends on avoiding the adoption of any principle which is not proven by many individual facts; by studying with care the character and course of diseases and by treating them according to the indications drawn from the observation of that which has succeeded in like cases. This is the method which Hippocrates asserts to have been known long before him, which he presents as the only way by which one may make real discoveries.**

In the same year he became a member of the *Société de l'Ecole de médecine*, the precursor of the *Académie de médecine*. He was likewise made an editor of the *Journal de médecine*.

In 1805 he published a valuable article on the classification of organic changes; this led to a distressing quarrel with Dupuytren, which lasted for several years. He was feverishly active, working day and night. Delicate, rather frail physically, he was very fond of out-door sport for which, alas, he had small opportunity, and his uninterrupted studies told upon his health. The happy presence of a cousin, Madame de Pompéry, at the *Château de Courrelles*, near Soissons, afforded him the opportunity for a much needed vacation. Rouxeau, in his biography,[2] gives a charming account of his visit, during which he met the young woman who was later to be his wife. This account bears interesting testimony to his social charms and to the ease with which he wrote really rather clever verse.

In 1812 he was made *médecin suppléant* at the Beaujon. In 1814 he was attending physician at the Salpêtrière which was then a military hospital. In 1805 he had taken up the study of the native tongue of his people and had acquired a reading and speaking knowledge of the Celtic dialect of lower Brittany.

[2] Rouxeau, Alfred: Laennec avant 1806, 8°. Paris, Baillière et fils, 1912.

In 1814 there were, in the Salpêtrière, many young Breton conscripts, wholly unable to speak French and wretchedly home-sick. To these poor fellows Laennec was a God-send. "More than one," says Rouxeau,[3] ". . . . doubtless owed his recovery to the joy of finding in Paris a compatriot who knew so well how to comfort them in their maternal tongue."

In 1816 he became chief of service in the Hôpital Necker. It was in this year that he made his famous discovery of the stethoscope. The story has been told so often that one need not repeat it here. With the introduction of the stethoscope and the revelations following its use, he began immediately to accumulate the material which later formed his book. Under the strain of his increasing practice and his constant and engrossing studies, his health began seriously to give way, and in August, 1818, he took a vacation of several months in Brittany, whence he returned on the 1st of November. While correcting the proof of his book, he was at the same time busy with the manufacture of his stethoscopes. Professor Rouxeau tells me that it is probably true that all the stethoscopes in existence at the time of his death were made by Laennec himself. Working with a lathe in his own room, he sought to prepare enough instruments so that whosoever bought the book might have a suitable implement with which to pursue his studies.

In these days of prolific terminology, when so many of us coin with delight strange, new, and often barbarous words to express simple things, it is interesting to know that Laennec, who wrote and spoke clearly and simply himself, resisted the introduction of any term for the instrument beyond the simple word "cylinder." Others, however, sought to name the implement for him, and in the end, somewhat reluctantly, he gave way, modifying the term "thoraciscope," suggested by his uncle Guillaume Laennec, by substituting the other Greek root.[4]

About August 15 the book finally appeared, marking, as Rist[5] has well pointed out, the beginning of modern clinical medicine.

But in its precious folds were imprisoned the heart's blood of its author, and on the 16th of August he writes to his colleague Pérusel of his suffering, his *"hypochondrie, goutte, asthme"* and says: "I am determined to abandon medicine and Paris and retire to Brittany, where few patients, I hope, will be tempted to seek me." At the end of the year, exhausted and suffering from that "asthma" which but too clearly must have been the beginning of his fatal illness, he retired to Kerlouarnec where he spent two years in rest and recuperation.

But he could not resist the call of life and activity in the capital. Health, or the semblance of health returned, and early in 1882, he reappeared in Paris to find himself appointed physician to the Duchesse de Berri, an honorable post but not a sinecure. He was soon made professor of medicine at the *Collège de France*. His practice became arduous. His lectures at the university were carefully prepared and revised, as is testified to by the notes which remain. The first of these, delivered on the 22d of August, 1822, forms the introduction to the *Archives générales de médecine*.

At that time Broussais, with his doctrine of irritation, held full sway. With him the clear-seeing Laennec could not fail to clash. Impetuous, ardent, dogmatic, eloquent, Broussais had a large and enthusiastic following, and the controversy between the two professors was celebrated. It is interesting to-day to read the fine, impassive, logical comments of Laennec upon the views of his fantastic adversary. While Broussais captured the popular imagination and had a large following, the real ability of Laennec soon made itself felt among the more thoughtful students. His clinic grew in popularity; his name became more widely known, but his health could not long stand the strain.

In 1824 he married Madame Guichard-Guéguen, veuve Argou, his devoted companion and house-keeper for many years. He was made a Knight of the Legion of Honour. Already in 1824 the first edition of his book had given out. With the new material that he had collected, Laennec had been busily engaged on a second edition in which the original book was almost rewritten. By May of 1826 the revision was finished, but its preparation had exhausted the physical capital of its author. At the end of June, he gave up his work in Paris and returned to Kerlouarnec, where he died on August 14 at the age of 45.

It was a life of great achievement. He had made important contributions to anatomy; he had taken his place among the great pathological anatomists. He had been the first, anatomically and clinically, to describe peritonitis, bronchitis, emphysema, pulmonary œdema, pulmonary apoplexy. He was the first accurately to describe the character of the sputa in pneumonia, and his pictures, anatomical and clinical, of pneumonia and of pulmonary tuberculosis will always remain classics. His methods of clinical study have never been surpassed, and stand a model for the clinician of to-day. He might almost be called the father of modern clinical medicine. For with all the work of Auenbrugger and Corvisart, the art of physical diagnosis hardly existed before Laennec.

Personally he was a small, rather delicate looking man, with curly chestnut hair. The face was rather thin and oval with a particularly long, typically Celtic upper lip, which is striking in the bust of Toulmouche at Nantes. Last summer, through the courtesy of Professor Rouxeau, I had the happy chance of seeing not only this bust, but also the one good portrait of Laennec which exists. This portrait, painted by Dubois in 1812, is owned by his great-nephew M. Robert Laennec, who most graciously received us at his charming place in the suburbs of Nantes. The picture is life-like; one feels that it must have been a good portrait. The face and figure are most interesting. The expression, somewhat *narquois*, is attractive—a fine, witty, rather whimsical look. Although the man seems small and thin and delicate, yet the long, pointed, typically Irish upper lip and something about the mouth give a strong suggestion of vigour and spirit and humour. One can well fancy his physical energy. 'Tis a striking painting of an engaging figure.

The three letters which follow were written to an old school

[3] *Op. cit.*

[4] Rouxeau: Paris méd., 1919, XX, No. 44, III.

[5] Rist, E.: Presse méd., Par., 1913, XXI, 357.

mate, Dr. Courbon Pérusel, of Carhaix, in Finisterre, who has consulted him because of a "*dartre*," a term which, in those days, evidently covered a large variety of cutaneous manifestations from simple seborrhœa and senile keratosis to graver affections. 'Tis clear from the context that the good fellow's annoyance was based largely on moral compunctions as to the justification of his contemplated matrimony. Laennec endeavours to reassure him, and upbraids him for what he considers purely hypochondriacal fancies. But it is three years before Pérusel is convinced; and before he can persuade himself that he is justified in taking the momentous step, he has consulted the fashionable dermatologist of the day, Jean Louis Alibert, with regard to whose methods Laennec expresses himself with some severity.

BUST OF LAENNEC BY TOULMOUCHE (1844), TAKEN FROM PARIS MÉDICAL, NOVEMBER, 1919.

The first letter was begun on the 22d of April, 1817, and the first folio, in which Laennec gives so vivid a description of his busy life, is written evidently at one sitting, one might fancy before going to bed. The next four pages are written on separate sheets. The fourth page ends with the words: "*Je crois qu'en—.*" The fifth page continues the sentence, "*somme, on ne doit,*" etc., but is written with another pen and in a somewhat different form, clearly at another time. The sentence is finished, however, before the confession which follows in two lines, in the shape of a new date "*29 Avril,*" and an acknowledgment that there has been a week's interruption in the letter. How many of us have done the same!

The second letter in which he speaks of his intention to retire to Brittany, is written on the 16th of August, 1819, the very day after the publication of his book. The third, fourth, fifth, sixth and seventh lines are in great part erased, "scratched out," the erasures apparently made by his own pen. By careful study with a lens it has, however, been possible to discover the original text. The same is true of his later reference to Alibert. The several words erased in the thirteenth line of the second letter I have not been able to read.

Paris 22 avril 1817.

Je vous demande mille pardons, mon cher Forest, d'avoir tant tardé à répondre à votre lettre du 28 février que j'ai reçue le 9 mars. Depuis ce jour il n'a pas passé un seul que je ne me proposasse de vous écrire le lendemain. je vous dois des excuses pleines et entières, car je suis honteux d'avoir été tant de fois en arrière vis à vis de vous et en conséquence je dois vous expliquer en détail comment il se fait que le plus grand désir de savoir des nouvelles de mes amis et même de leur écrire je finis presque toujours par ne leur jamais écrire que dans les cas de la plus urgente nécessité. il faut pour cela vous expliquer mon genre de vie. je me lève à 7h½ ou même à 8h car j'ai besoin de beaucoup de sommeil. je m'habille le plus souvent en donnant des consultations. je vais faire ma visite à l'hôpital (à l'hôpital necker) il me reste un bout de clinique aux élèves qui le suivent. cela me mène à 10h½ et déjà le temps me presse assez pour que le plus souvent je ne puisse pas rentrer chez moi pour déjeuner: je commence donc une tournée qui ne finit que vers 5h½. après dîner, c'est à dire vers 6h½ j'en recommence une autre jusqu'à 10h. il me reste ensuite une heure jusqu'à 11h que je cède quelques minutes de temps en temps avant le déjeuner et le dîner, pour tenir à jour mes correspondances de toute espèce, corriger et mettre en ordre les observations recueillies par les élèves dans mon hôpital, régler mes petites affaires &c. &c. cette première vue vous donne quelque faible idée de ce que c'est pour un homme un peu occupé, que le tourbillon de relations de toute espèce dans lequel on se trouve emporté à paris, quelque soin qu'on mette à les simplifier. j'ai souvent été étonné que vous et quelques autres de nos confrères vous fussiez retirés dans de très-petites villes. aujourd'hui je vous loue et approuve très-fort et je songe moi-même sérieusement à arranger mes affaires de manière à pouvoir sous très-peu d'années me retirer en basse bretagne si j'avais ce que mérite dû ici, elle ne serait pas déjà aujourd'hui.

Je viens à la question sur laquelle vous me consultez. je ne conçois pas que vous puissiez la délicatesse à une pareille extrémité. la contagion des dartres dans les cas les plus graves existe, est assurément très-obscure. je le sais de l'application immédiate et continuée pendant quelque temps d'une dartre phagédénique en pleine suppuration produirait autre effet que celui d'un rubéfiant, mais je sais bon nombre de maris qui ont des dartres invétérées avec certitude sans avoir jamais rien communiqué à leurs femmes et vice versâ. quant aux dartres furfuracées comme les vôtres, un bon tiers du genre humain en est attaqué à une époque quelconque de la vie, et après 60 ans, il n'y a guères d'individu sur lequel on n'en trouvât en cherchant bien. la peau de l'extrémité de la main à cet âge fait qu'on se

* The letters are reduced to one-half their original size.

porte le plus souvent sans s'en douter.

Si l'on s'en rapportait à l'opinion de la plupart des dartreux et dartreuses, ils auraient contracté toute affection par contagion : mais en observant avec un peu d'attention, on voit bientôt que sous le rapport du caractère propre de l'affection les dartres se rapprochent par des nuances insensibles d'autres affections dans lesquelles on ne s'est jamais avisé de supposer la contagion et particulièrement de certaine variété de l'erysipèle à marche chronique. 2° que tous le rapport étiologique pour un cas où l'on pourrait soupçonner la contagion, on en voit des milliers qui prouvent le contraire ; que chez un très-grand nombre d'individus, les dartres sont le produit d'un mauvais régime et particulièrement de la misère, de la mal propreté, des veilles trop habituelles, des excès d'alcool, de table, de l'impression habituelle du froid ou de l'humidité (chez les ouvriers) et en général de toutes les causes qui dérangent la tranpiration insensible). or les maladies réellement et absolument contagieuses, la gale, la teigne, la petite vérole, la scarlatine, la syphilis ne se produisent point par des écarts de régime, on ne doit même appeler contagieuses que celles qui sont épidémiques et endémiques les maladies dues à des erreurs analogues qui se propagent le plus rapidement, comme la typhoïde des camps et hospitaux ; car quelquefois on a dit pour établir l'existence de la contagion dans ces cas, on a prouvé seulement que trois ou quatre malheureux réunis d'hommes vicieux ou malades dans un lieu trop étroit font naître un foyer d'infection dans lequel on ne peut pénétrer et quelquefois même aborder sans y contracter une fièvre grave à la quelle on a vainement cherché des caractères propres, car ils varient dans chaque épidémie. Ignorer les malades, donner le change d'eau de l'espace et des soins de propreté la prétendue contagion cesse. qui oserait propager un pareil reproche contre la teigne et la petite vérole ?

pour revenir aux dartres, il me semble que les faits rencontrent que presque tous les hommes y sont disposés plus ou moins ; que beaucoup d'enfants nés de parents non dartreux en sont affectés dès leur bas âge (il en est même des scrofuleux) ; que d'autres sujets en contractent aux diverses époques de la vie par suite d'erreurs hygiéniques, et que la vieillesse surtout, à la moins susceptible de contracter les contagions les moins chez beaucoup de gens qui n'en avaient jamais eues. je pense qu'on doit les regarder quand elles sont à un degré médiocre et qu'elles ne sont pas dues à des causes accidentelles, comme une simple incommodité produit d'un défaut d'équilibre dans une constitution d'ailleurs très-bonne. je les comparerais sous ce rapport aux scrofuleux qui lorsqu'ils existent à un très-léger degré chez des sujets d'ailleurs sains et robustes ne sont réellement que l'excès d'une constitution d'ailleurs la meilleure du monde, le tempérament lymphatico sanguin, et ne sont appelés que par les médecins. les dartreux naissent comme les scrofuleux chez des sujets de parents exempts de ces affections : mais l'une et l'autre affection se communique quelquefois par l'organisation comme la constitution même des parents, leur physionomie et leur port de vais. je crois qu'on

homme, on ne doit les regarder comme une maladie à traiter que quand elles sont très-fortes.

29 avril j'avais daté ma lettre du 22 courant espérant l'avoir terminée ce jour là. nous voici à la fin du mois et je n'ai encore pu terminer cette lettre écrite comme tout ce que j'ai fait, à bâtons rompus. il faut pourtant que vous ne l'attendiez pas davantage la dose en étant achevé n'en vaut pas la peine et je vais la terminer en vous disant deux mots de ce qui m'a le mieux réussi en fait de traitement.

Je n'ai jamais retiré aucun effet sensible de la scabieuse, de la fumeterre, de la racine de pensée sauvage (que j'ai pu employer des préparations d'antimoine. Les antiscorbutiques m'ont paru avoir quelque avantage dans les dartres scrophuleuses, la sublimé dans les cas où l'on peut supposer une principe syphilitique héréditaire. la douce amère m'a servi merveilleusement dans deux ou trois cas de dartres croûteuses très-intenses : mais dans une multitude d'autres cas, je n'en ai obtenu rien, quoique poussée graduellement à la dose de 2 à 6 onces pour trois verres de décoction, que la malade prenait chaque jour et continuée pendant six mois et au delà.

à dose aussi forte et même à deux onces j'ai vu produire chez quelques individus un spasme tonique d'un côté de la face, avec distorsion de la bouche et parole embarrassée qui au premier abord aurait pu être prise pour un tique d'habitude épileptique et accident cessé en trois ou 4 jours en interrompant le remède.

De tous les dépuratifs celui qui m'a le mieux réussi, c'est l'usage des bains sulfureux préparés avec trois onces de sulfure de potasse solide pour un bain auquel on ajoute en outre un demi-verre de vinaigre ou le gros de l'acide sulfurique dans votre cas je me contenterais de prendre une vingtaine de ces bains aux mois de mai, août et 7bre et celui en prendrait plusieurs années de suite il le faudrait et je prendrais ces autres pendant un temps [illegible] les bouts, deux verres d'eau sulfureuse immédiatement d'heure avant chaque repas suivant la formule suivante

℞. foye de soufre solide 3i
sucre
faites fondre dans 3 ju
eau chaude 16 ij
mettez en bouteille boucher et
agiter chaque fois qu'on en fait usage.

je me suis délivré il y a déjà deux ans de deux dartres purpurines vineuses par cet heureux remède à haute dose continué huit mois et

l'usage de la liqueur sulfureuse ci-dessus mais d'après ce que j'ai obtenu depuis de succès et de non succès, si pareille chose se présentait encore je préférerais les bains

Si quelque dartre se trouvait sur une partie d'où il fut bon de la déplacer le plutôt possible, comme la figure, le sein de la femme &c je vous conseillerais de la toucher légèrement avec la pierre infernale ; ce procédé qui au fond ne fait que changer la nature de l'inflammation est sans inconvénient. j'ai vu ici un malade âgé de 80 ans qui a été guéri à 56 de dartres étendues par l'usage de l'huile de tartre par défaillance que l'on étendait avec une petite plume sur l'éruption. on la coupait d'abord avec 3/4 d'eau et on finit par l'employer pure le traitement interne employé en même temps n'équivalait à rien pour avoir le temps de m'étendre davantage, mais intelligenti pauca

j'ai fait dans le temps des démarches pour voir votre père ; mais j'appris de voir que l'attachement aux principes n'était pas un titre de recommandation auprès du bien des gens et rien n'a changé encore ici à cet égard.

j'ai été bien affligé de n'avoir pas 3 ou 4 jours à moi lorsque j'ai été à Grasse en 1814. [redacted] je me proposais d'y aller faire un tour l'année prochaine et cette fois j'espère bien pourrais m'arranger de manière à vous aller voir. je vous embrasse de tout mon cœur

Votre compère et ami

Alex Lavenue Duval

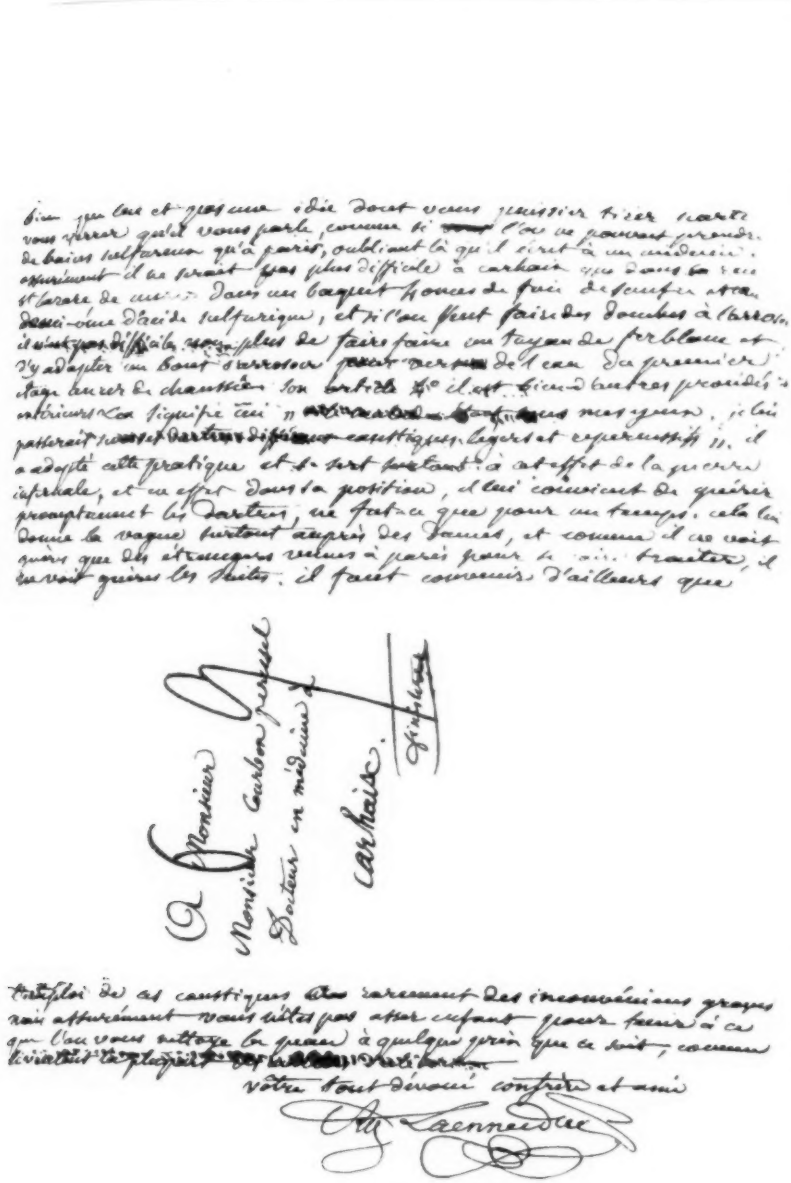
A Monsieur
Monsieur Caffe Fenwick
Docteur en Médecine à
Orléans
Loiret

Paris 16 août 1819.

je ne conçois pas, mon cher Fenwick, vos inquiétudes sur le fond et les circonstances des très-légères incommodités que vous éprouvez. [redacted] ; je vois ici [redacted] ; [redacted] et Paris et à me retirer en Bretagne où quelques malades, j'espère, seront tentés de venir me relancer. je pars d'ici vers les 7bre et probablement j'aurai le plaisir de vous voir en 8bre car une petite affaire me conduira à Orléans et je passerai certainement en allant ou revenant par Carbonnières nous pourrons alors causer à loisir [redacted].

De votre place je ne balancerais à prescrire tous les ans une trentaine de bains sulfureux aux printemps et autant en automne pour atténuer les dartres et je ne chercherais pas à m'en débarrasser tout à fait de peur de pis. quant à la crainte de la contagion je suis réellement scandalisé (médicalement parlant) que cela vous tracasse encore dans la tête. en bonne conscience, si j'avais une fille ou une sœur à marier votre état ne m'empêcherait nullement de vous la donner. les dartres, les scrophules, la phthisie, et beaucoup d'autres maladies ne sont reconnues d'être contagieuses que parce qu'elles sont très-communes, et un examen attentif des faits détruit facilement ce soupçon.

j'ai communiqué votre mémoire à Alibert. [redacted], je lui ai dit qu'il s'agissait d'un confrère afin de fixer d'avantage son attention et en conséquence je vous renvoie votre mandat. vous verrez que cela n'a pas servi à grand chose : car il vous a donné comme à un autre une formule banale de consultation, où vous trouverez tout ce que vous savez aussi



Kerlouarnec par Douarnenez 18 janvier 1820

J'ai reçu en son temps, mon cher Parmentel, votre lettre du mois dernier, à laquelle la vie errante que je mène ici pendant que l'on rebâtit à neuf mon hermitage, m'a empêché de répondre plutôt.

J'avais appris par Tocalgoët votre mariage, et je vous en félicite d'autant plus sincèrement que je sais que vous êtes homme à apprécier toutes choses à leur valeur véritable, ce qu'on ne peut pas dire de tous les gens qui se marient. il m'est vrai cependant à laquelle vous donner, à mon avis, beaucoup trop d'importance; c'est le cas de médecine dont vous me parler. je ne puis vous blâmer d'avoir suivi le conseil d'Alibert quoique (entre nous) vous pouvez être sûr qu'il l'a donné aussi légèrement que pratique tout ce qu'il donne au public, mais

je crois que vous ferez bien de vous en tenir là pour le moment et surtout d'être réservé sur l'usage des dépuratifs minéraux. vous savez comme moi que le long usage du sirop d'iodure détermine quelquefois des crachements de sang, et vous connaissez tout aussi bien les inconvéniens d'un genre différent des préparations d'hydrargyre.

optima est abstinentia medicina, medicina non agere. je [illegible] jouer mon compte et pour celui d'autrui (quand je trouve les gens assez dociles) cette maxime de celse, dans tous les petits maux qui sont beaucoup plus difficiles à guérir qu'à supporter, et je vous conseille en ami d'en faire autant.

j'irai au Faouët, vous savez à ce sujet, comme je vous l'ai promis et j'espère que cela sera

bien que cet projet ait pu vous paraître [illegible] vous parle comme si [illegible] de baies salsepareuse qu'à Paris, oubliant là que l'iode [illegible] assurément il ne serait pas plus difficile à [illegible] et [illegible] dessiccative d'acide sulfurique; et si l'on peut faire des doubles à [illegible] il suffirait [illegible] de faire faire un tuyau de fer blanc et d'y adapter un bout d'arrosoir percé [illegible] de l'eau de goudron [illegible] chantier [illegible] bouteille [illegible] extérieurs. Cela signifie [illegible] mes yeux. je lui [illegible] et [illegible] différens caustiques, légers et expectorants. il a adopté cette pratique et [illegible] à cet effet de la guerre infernale, et en effet dans la position, il leur convient de guérir promptement les [illegible], ne fut-ce que pour un temps: cela lui donne la vogue surtout auprès des femmes, et comme il ne voit guères que des étrangers venus à Paris pour se faire traiter, il ne voit guères les suites: il savait convenir d'ailleurs que

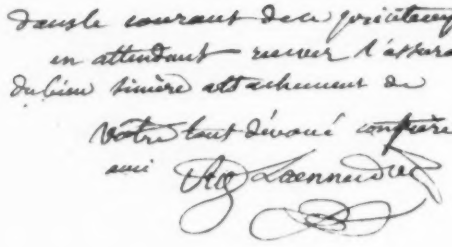
A Monsieur
Monsieur Carbon Parmentel
Docteur en médecine
à
Carhaix.

[illegible] de ces caustiques [illegible] rarement des inconvéniens graves soit assurément vous n'êtes pas assez enfant pour tenir à ce que l'eau vous entoure le genou à quelque prix que ce soit, comme [illegible] votre tout dévoué confrère et ami

By means of the lens it has been possible to decipher the third, fourth, fifth, sixth and seventh lines which have been in great part erased, as well as the reference to Alibert in the seventh line from the bottom of the page. These lines should read as follows:

"pour moi, je me bornerais volontiers à n'en pas avoir d'autres. il est vrai que j'en ai tout autant que vous, ou peu s'en faut, et de plus, de l'hypochondrie, de la goutte, de l'asthme; tant y-a-t'il que je suis déterminé à abandonner la médecine = "

The seventh line from the bottom of the page should read: "comme il est toujours aussi léger que vous l'avez connu,"



First letter written to,
M. Courbon Pérusel,
Doctor of Medicine at,
Carhaix, Finisterre,

PARIS, 22 April, 1817.

I beg a thousand pardons, my dear Pérusel, for having so long delayed in answering your letter of the 28th of February, which I received on the 8th of March. Ever since that day not one has passed without my having intended to write to you on the following day. I owe you full and entire apologies, for I am ashamed to have been so often in arrears to you, and consequently I am going to explain to you in detail how it comes about that with the greatest desire to learn all the news of my friends and even to write to them, I end almost always by writing to them only in the case of the most urgent necessity. In order to do this I must explain to you my manner of life. I rise at half past seven or even at eight o'clock, for I need much sleep. I dress myself, generally, while giving consultations. I make my hospital visit (at *l'hôpital Nécker*) and then a bit of clinic to the students who follow me. This brings me to half past ten, and already time presses me to such an extent that generally I cannot return to my house for luncheon. Then I begin a round of visits which ends only at about half past five. After dinner, that is to say at about half past six, I begin another round which lasts till ten o'clock. There then remains for me one hour until eleven when I go to bed, plus several minutes from time to time before breakfast and dinner to keep up-to-date my correspondence of all sorts, to correct and put in order the observations gathered by the students in my hospital, to arrange my little affairs, and so forth. This picture gives you but a feeble idea of that which, for a man who is rather busy, is this whirlwind of relations of all sorts in which one finds himself carried away in Paris, however hard one tries to simplify them. I have often been astonished that you and some others of our confrères should have retired to very small towns. To-day I applaud you and approve very strongly. For myself I think very seriously (*entre nous*) of arranging my affairs so as to be able, in a very few years, to retire to lower Brittany. Had I that which was due me here it would probably be to-day.

I come to the question on which you have consulted me. I can not see how you can push your delicacy to such an extremity. The contagious nature of *dartres* in the gravest cases is certainly very obscure. I know not if the immediate and continued application during a period of time of a phagedenic dartre in full suppuration could produce an effect other than that of a rubefacient, but I know a good number of husbands who have exudative *dartres* on the scrotum without having communicated anything to their wives, and *vice versa*. As for furfuracious *dartres* like yours, a good third of the human race is attacked at one period or another of their lives, and after 60 years there are no individuals on whom one may not find them if one search well. The slight sensitiveness of the skin at this age brings it about that people have them generally without suspecting it.

If one were to turn to the opinion of the greater part of the men and especially the women affected with *dartres* they would have it that they had all contracted the affection by contagion, but on observing with a little care, one sees, 1°, that considering the essential nature of the affection *dartres* approach by insensible nuances other cutaneous diseases of which we have never thought of suspecting the contagiousness, and particularly certain varieties of erysipelas of a chronic course. 2°, that from an ætiological standpoint, for one case in which one might suspect contagion one sees thousands which prove the contrary; that in a great number of individuals *dartres* are the product of a bad régime and particularly of want, of uncleanliness, of too habitual loss of sleep, of excesses in study, of excesses of the table, of habitual exposure to cold or humidity (in certain workmen) and, in general, of all those causes which disturb the insensible perspiration. But the diseases really *et absque dubio* contagious, *e. g.*, plague, smallpox, contagious itch, syphilis, do not arise from transgressions of régime. One should not call *contagious*, but epidemic and endemic those diseases due to analogous errors which spread most rapidly, such as typhus of camps and hospitals; for whatever has been said to establish the existence of contagion in these cases, it has been proved only that a reunion of too many healthy or diseased men in too restricted an area gives rise to a centre of infection which one may not frequent or sometimes even approach, without contracting there a grave fever for which one has vainly sought specific characteristics, for they vary in each epidemic. Separate the patients, give each one of them space and attention as to cleanliness, and the supposed contagion ceases. Who would dare to propose a like remedy against plague and smallpox?

To return to *dartres*, it seems to me that the facts show that almost all men are more or less subject to them; that many children born of non-dartrous parents are affected with them in their early age (the same is true of scrofula); that others contract them at various periods of their life as the result of hygienic errors, and that old age, the age least susceptible to contagious diseases, brings them to many people who never have had them. I think that when they are of moderate degree and not due to accidental causes, one should regard them as simple incommodities, the result of a loss of equilibrium in a constitution in other respects very good. I should compare them from this point of view to scrofula, which when it exists to a slight degree in a subject in other respects healthy and robust, is really not more than the excess of a constitution which is indeed the best of all, the lymphatico-sanguine temperament, and is recognized only by the physician. *Dartres* arise as does scrofula in infants born of parents free from these affections. But both of these diseases are communicated sometimes by generation as is the very constitution of the parent, their physiognomy and the sound of their voice. I think that[6] on the whole one should not regard them as a disease *to treat* excepting when they are very severe. *29 April*—I had dated my letter the 22d current hoping to have finished it on that day. Here we are at the end of the month and I have not yet been able to finish this letter written, as is everything that I do, in broken periods. You must not, however, wait for it longer. The affair, indeed, is not worth the trouble, and I am going to finish by saying two words to you concerning that which has given me the greatest success from a point of view of treatment.

I have never accomplished any appreciable effect with *scabiosa*, with *fumaria*, with the root of wild pansies (which I have employed but little), with preparations of antimony. Anti-scorbutics have seemed to me to have some value in scrofulous *dartres*, sublimate in cases in which one may fancy a syphilitic base. I have had *remarkable* success with bitter almond in two or three cases of scaly *dartres* of great intensity: but in a multitude of other cases, I have obtained *no* results, although pushed gradually

[6] Here ends the fourth page of the manuscript. The continuation on a new sheet is written with a different pen and clearly at a later date.

to a dose of *3 to 4 ounces* for three glasses of decoction, which the patient took each day and continued during eighteen months and more thereafter. At a dose so large as this and sometimes even of two ounces I have seen it produce in some individuals a tonic spasm of one side of the face, with distortion of the mouth and embarrassment of speech, which at first glance might have been taken for a sign of hemiplegia. This accident ceases in three or four days on interrupting the remedy.

Of all the depuratives that which has given me the best results is the use of sulphuric baths prepared with three ounces of solid sulphate of potassium for a bath, to which is added besides, a half glass of vinegar or four drachms of sulphuric acid. In your case I should content myself with taking twenty of these baths in the month of May, as many in September, and this for several years if it should be necessary. And I should take in addition for a longer time, that is say 3 or 4 months, a glass of sulphurous water a quarter of an hour before each repast according to the following formula:

℞ Solid sublimated sulphur.....3 i
Sugar .....3 iv
Dissolve in hot water.....0 ii
Put in bottle, cork and allow to cool.

I freed myself ten years ago of two furfuracious, scaly *dartres* by bitter almond in large doses continued eight months and the use of the above sulphurous fluid. But from the successes and the non-successes, if indeed I have had these, which I have obtained since then, I should prefer the baths.

If a *dartre* should exist in a region where it were well to remove it so soon as possible, on the face or at the corner of the mouth, etc., I should advise you to touch it lightly with nitrate of silver; this procedure which at the bottom, but changes the nature of the inflammation is without inconvenience. I have used it upon myself. I have seen here a patient of 80 who was cured at 56 of extensive *dartres* by the use of deliquesced oil of tartar ("par défaillance") which was painted upon the eruption with a brush. It was first diluted with three-fourths water and in the end employed pure. The internal treatment employed at the same time was of no significance. I wish I had the time to go into the matter more extensively, but *intelligenti pauca*.

I have taken some steps recently to assist (?) your brother. But I had occasion to observe that attachment to "*principes*"[7] was not a title of recommendation with many people and nothing has yet changed here in this respect.

I was much vexed not to have three or four days to myself when I was in Quimper in 1814. I propose to go there on a trip the coming year and I hope sincerely that this time I may arrange to be able to visit you. I embrace you with all my heart.

Your confrère and friend,
R. T. H. LAENNEC, D. M.

Second letter, written to,
M. Courbon Pérusel,
Doctor of Medicine at,
Carhaix, Finisterre,

PARIS, 16 August, 1819.

I can not conceive, my dear Pérusel, your anxieties as to the essence and the circumstances of the very trivial inconveniences from which you are suffering. (So far as I go I should be well content to have nothing more. It is true that I have fully as many as you, or approximately, and in addition hypochondriasis, gout, asthma, and so forth; so much, indeed that I am determined to abandon medicine)[8] and Paris and to retire to Brittany where few patients I hope, will be tempted to seek me out. I am leaving on about the 16th of September and probably I shall have the pleasure of seeing you in October, for a small affair will bring me to Morlaix and I shall certainly pass through Carhaix in going or returning. We can then speak at leisure.[9]

In your place I should restrict myself to taking yearly thirty sulphurous baths in the springtime and as many in the autumn to attenuate the *dartres*, and I should not endeavour to free myself entirely for fear of making things worse. As to the fear of contagion I am really *scandalized* (medically speaking) that such an idea still runs in your head. On my conscience, if I had a daughter or a sister to marry, your condition would hinder me in no way from giving her to you. *Dartres*, scrofula, phthisis, and many other diseases are suspected of being contagious only because they are very common, and a careful examination of the facts destroys this suspicion very easily.

I have communicated your memorandum to Alibert. (As he is always as frivolous as you have found him)[10] I told him that it was the question of a colleague in order better to fix his attention, and as a result I am sending you your prescription. You will see that my precautions have not been of great service: for he has given you, as he would to another, a common formula of consultation, where you will find that which you know as well as he and not an idea from which you may profit. You will see that he talks to you as if one could not take sulphurous baths excepting in Paris, forgetting in this that he is writing to a physician. Certainly it would not be more difficult at Carhaix than in the Rue St. Lazare to put into a bucket 4 ounces of sulphur and one-half ounce of sulphuric acid, and if one wishes to prepare douches for spraying, it is not difficult to have made a tube of white metal and to fit upon one end a spray to convey the water from the first storey to the ground floor. His article 4° *there are indeed other early procedures*, etc., signifies this: "If the patient were under my observation I should apply to his *dartres* different mild caustics and repercussives." He has adopted this practice and makes use especially of nitrate of silver, and indeed in his position it is desirable to cure *dartres* promptly even if it were only for a time. This gives him the vogue especially with the ladies, and as he sees only strangers who come to Paris to be treated, he never sees that which follows. One must acknowledge, however, that the use of these caustics rarely has grave inconveniences. But certainly you are not such a child as to desire that your skin be clean at whatever price as do the greater part of the patients of Alibert.

Your ever devoted confrère and friend,
R. T. H. LAENNEC, D. M.

Third letter.

KERLOUARNEC PAR DOUARNENEZ, 18 January, 1820.

In its time, my dear Pérusel, I received your letter of last month, to which the wandering life that I am leading here, while they are almost completely rebuilding my hermitage, has hindered me from answering earlier.

I had learned through Toulgoët of your marriage, and I congratulate you, all the more sincerely in that I know that you are a man who can appreciate all things at their true value, that which one cannot say of all people who marry. There is one thing, however, to which in my opinion you ascribe far too much importance: namely, the question of medicine of which you speak to me. I cannot blame you for having followed the advice of Alibert, although (between us) you may be sure that he gave it to you as frivolously as almost all that which he gives to the public: But I think that you would do well to stop there for the moment, and especially to be guarded in the use of mineral depura-

[7] Underscored in the original. Are we, perhaps, to accept the word in its Latin sense?

[8] These lines are erased by heavy marks of his pen.

[9] Here several words are crossed out so successfully that one is unable to read them.

[10] Erased but deciphered with the lens.

tives—you know as do I that the long use of sulphur sometimes brings about blood spitting, and you know equally well the inconveniences of another sort of the preparations of mercury.

*Optima interdùm medicina, medicinam non agere.* For my own account and for that of others (when I find the people intelligent enough) I follow this maxim of Celsus, in all the little ills which are much more difficult to cure than to endure, and I advise you as a friend to do the same.

I am going to lecture you, however, on this subject, as I promised, and I hope that this will be in the course of the spring.

In the mean time accept the assurance of the sincere attachment of your devoted confrère and friend

R. H. T. Laennec, D. M.

There is much in these brief lines on which one might comment or moralize. Especially interesting is the reference in the second letter to the non-contagiousness of phthisis. Laennec is very careful in his statements as to the contagiousness of tubercle. In the manuscript notes for his twentieth lecture at the *Collège de France,* which I was able to examine last summer through the great kindness of Dr. Cornillot, I find the following entry: *" Tuberc. sont il contag.? Contag. des scrophules et des tuberc. crus dans bp de pays. mesures administr. Faits pour et bp plus contre. Observ. de tub au doigt par inocul. ne pas trop s'y fier: mais certes pas facilement contag. en nos climats:"*

But later there is added with another pen: *" Toutes les malad. contag. peuvent l'être plus ou moins. petite vérole, syphilis, peste elle même, moins vers la fin d'épid, mais contag. n'est pas moins certaine."*

This might be translated " Are tubercles contagious? The contagiousness of scrophulosis and of tubercles, believed in many countries. Administrative measures. Facts for and many more against. Observation of tuberculosis on the finger by inoculation. Don't rely on it too much: but certainly not easily contagious in our climate. . . . . all contagious diseases may be so more or less—small-pox, syphilis, plague itself, less toward the end of epidemics, but contagious none the less certainly."

In the second edition of his book he discusses the question in much the same way. " Tuberculous phthisis," says he,[11] " has long been considered contagious and is now so regarded in the popular mind, and in the opinion of magistrates and of some physicians in certain countries, and especially in the southern parts of Europe. In France at least, it does not seem to be. One sees often among people of moderate circumstances, a large family sleeping in the same room with a phthisical patient, a husband sharing to the last moment the bed of his phthisical wife without contracting the disease. The woolen clothes and mattresses of the phthisical, which in certain countries are burned and which in France, as a rule, one does not even wash, have never seemed to me to convey the disease to anyone. However, prudence and cleanliness would demand more precautions than are usually taken in this respect. Many circumstances, however, prove that a disease which is not habitually contagious may become so under certain circumstances." He then goes on to ask whether a direct inoculation may produce the disease at least locally, and describes an instance in which he infected himself at a necropsy with the subsequent development of an anatomical tubercle. Later he says: " If the question of contagion may be regarded as in doubt with relation to tuberculosis, there is no doubt as to hereditary predisposition."

It is interesting and remarkable that, with his clear recognition of the manner of spread of chronic tuberculosis in the lungs, the repeated fresh outbreaks following so often the softening of caseating areas, the idea of direct inoculation should not have imposed itself upon him more forcibly.

The reference in his first letter to the development of facial spasm following the prolonged used of oil of bitter almond is also interesting. Laennec was so careful an observer that any such statement deserves consideration. I have, however, found no support for the assertion in the literature.

The same might be said of his statement with regard to the influence of sulphur in inducing hæmoptysis.

The notes of his lectures at the *Collège de France,* half of which are in the possession of the *Ecole de médecine,* half owned by his great nephew in Nantes, are written on small quarto sheets, 12 cm. square. Each page is divided into two columns, the division apparently made by folding rather than by ruled lines. The main substance of the lecture is in the right-hand column; the space on the left is reserved for notes entered in a small, close hand. The lectures are not written in full. They are rather in the nature of carefully prepared memoranda. Laennec wrote a sort of personal short hand. Many words are abbreviated. Much is in Latin, which is also abbreviated. Some of his abbreviations are interesting. In the termination *" ation "* the *" ti "* is often omitted, as in old Latin texts, and written *" aon,"* *" dans "* is written *" ds,"* *" beaucoup "* is written *" bp,"* *" quelquefois "* is almost always written *" qqfois."* Capitalization is often omitted, and punctuation is very crude. The latter peculiarities may, indeed, be noted in the letters which have been reproduced above. In the main his notes are not hard to read while he writes in French. His short-hand Latin is not so easy.

Some of his entries are interestingly epigrammatic. In his opening lecture are notes like this: *" Science, ce que l'on sait."* " Science, that which we know." *" théorie, manière de voir. on ne voir [sic] tout et surtout tout à la fois. Donc, indispensable. mais pas oublier qu'échaffaudage, s'en servir comme d'un instrum. prêt à le rejeter et changer dès qu'un fait résiste."* " Theory, way of looking (at things). We do not see all and especially all at one time. Therefore, indispensable. But not to be forgotten that, scaffolding, one must make use of, as of an instrument ready to throw it aside and change it so soon as a fact holds its own."

The notes of his twentieth lecture, that on tuberculosis, are deeply interesting. The kernel of the description of pulmonary tuberculosis in the second edition of his book is clearly discernible.

As one glances over the notes of his lectures he is impressed with the clearness of view, the remarkable objectivity and the

[11] Traité de l'auscultation médiate, 2me édition, Paris, Chaudé, 1826, I, 649 et seq.

sane and accurate ratiocination. The more one considers Laennec's career the more deeply is he impressed by the greatness of the man and the magnitude of his work. And in thought, in methods, in expression he had that clearness and simplicity that marks the truly great. Here are the closing words of his introductory lecture taken down from the notes in his own hand:

"As for me, I shall not quit the path traced by the medical observers who have successively increased the treasure of science from Hippocrates to our day. If I diverge from some of them I do not fear to say that 'tis from a leaning toward simple observation—even though I may be accused of empiricism. Corvisart was my master, and 'tis perhaps to him that I am indebted for a certain distaste for explanations and theories. I shall make every endeavour to present the facts alone and connected by their most striking analogies, and if sometimes I am obliged in their exposition, to have recourse to some theoretical, hypothetical views, I trust that it may be evident that I am not insisting upon them, and that I may never put forward my individual opinion for *science*—that is to say, *that which we know.*"

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Preceding the presentation of the above paper at the meeting of the Laennec Society on March 29th, 1920, in commemoration of the one hundredth anniversary of the publication of Laennec's book on Auscultation, Dr. Henry Barton Jacobs brought before the Society a complete series of the editions of this book with the possible exception of one or two English translations. Dr. Jacobs is preparing a bibliography of these editions with reproductions of title pages, etc., which will be published later.

# PLEURAL SPIROCHÆTOSIS

By V. R. MASON

*(From the Medical Clinic, The Johns Hopkins Hospital)*

The following case is reported not only as an example of a disease very rare in America but also as the first instance of spontaneous infection of the pleural cavity by Spirochæta bronchialis (Castellani) which has been recorded. Inasmuch as certain assumptions, which we have been forced to make in order to explain the sequence of events in this case, are not, at the moment, susceptible of definite proof, a brief discussion of the present status of Castellani's bronchitis will be added from which a comparison of the clinical course of that disease with the symptom complex presented by our patient may be made.

MED. No. 43919.—Gabriel Banks. White, *æt.* 16. Admitted to The Johns Hopkins Hospital, June 18, 1920.

The patient was born in Austria and came to America when one year old. He had always been a healthy boy. So far as he knows he had not been associated with any individuals who spat blood.

*Present Illness.*—In January, 1920, he had an acute febrile illness which was believed to be influenza. He was not very ill at the time but never recovered completely. His chief complaints were cough with a good deal of expectoration and a constant dull pain under the left shoulder-blade. The sputa were often very foul. During the months following the onset of his illness he was not able to work although he was not confined to bed. On May 23, 1920, he expectorated a small amount of bloody material. The next day he visited the dispensary. Examination at that time revealed remarkably little. A radiogram of the chest showed a few small shadows in the lower lobe of each lung. No sputum was obtained. June 5, 1920, the patient had a chill followed by high fever and severe pain in the left side of the chest. He also noticed marked breathlessness. From this time until admission the patient was very ill. He had exhausting attacks of coughing productive of a small amount of foul sputum. Each night he was delirious and had drenching sweats.

*Examination.*—The patient looked very ill. There were marked cyanosis and dyspnœa. He was very drowsy. The temperature is shown in Chart I. There was an occasional unproductive cough. The breath had a peculiar fœtid odor. There were typical signs of fluid and air in the left pleural cavity. A loud friction rub was audible in the right axilla. Examination of a small mucopurulent specimen of sputum disclosed no spirochætes.

A needle was inserted into the left pleural cavity and about 60 c. c. of pinkish, milky fluid were easily withdrawn. It had a peculiar fœtid odor unlike that of any empyema we had observed. It was examined without staining and found to contain large numbers of pus cells, a few well preserved erythrocytes, some cocci and bacilli and *many actively motile spirochætes.* Dark field illumination confirmed these observations. The majority of the spirochætes were two to three times the diameter of an erythrocyte in length, blunt or pointed at the ends, and actively motile. There were many rather thick coarse forms but a few were very gracile. The number of undulations varied, but on the average four to six were present. A stained smear (methylene blue) of the fluid showed large numbers of bacilli and cocci and many poorly stained spirochætes. No fusiform bacilli could be found.

Cultures of this fluid and of the fluid obtained at operation were sterile on blood-agar plates and in nutrient bouillon.

On June 19, 1920, a tube was inserted between the ribs (by Dr. A. S. Taylor) and about 700 c. c. of pus were removed. The pleural cavity was subsequently irrigated frequently through the tube with Dakin's solution until the fifth day after operation, when this procedure had to be discontinued on account of violent attacks of coughing followed by collapse probably occasioned by forcing the solution through the perforated lung.

Specimens of the drainage from the pleural cavity, on the second and fifth days after operation, contained spirochætes in fair numbers. No other organisms were seen and the fluid was again sterile on culture.

*Post-Operative Course.*—The patient was critically ill for several days and his temperature remained high. On the fifth day neosalvarsan (Billion) 0.45 gm. was administered intravenously. The following day the patient expectorated considerable amounts of bloody material which, however, contained no spirochætes. Improvement from this time was rapid. Injections of neosalvarsan were repeated June 27, July 1 and July 23, 1920. The patient gained in strength and his symptoms rapidly ameliorated. At the present date he has completely recovered except for slight discomfort caused by a partial left pneumothorax.

### COMMENT

We have made a careful search of the literature for cases similar to this—that is, for cases of bronchospirochætosis in which intrapleural complications have developed, but have been unable to find a single instance of empyema with the presence of spirochætes in the pus. Lancereaux,[1] however, has recently reported on an instance of hemothorax caused by a penetrating war wound of the chest in which the bloody fluid contained spirochætes in large numbers apparently in the absence of other micro-organisms. Symptoms of an infected hemothorax were present in his patient, but they were promptly ameliorated by arsenical therapy. He believes, therefore, that the spirochætes, probably introduced by the missile, were responsible for the symptoms and clinical course of his patient.

We believe that the illness of several months' duration which preceded the admission of our patient to the hospital was produced by an infection of the lungs with spirochætes. Unfortunately these organisms were not found in the sputum but satisfactory examinations were not made. Nevertheless, the clinical course of the disease and the results of physical examination were very similar to those of bronchospirochætosis. It is probable, therefore, that during an attack of coughing an area of pulmonary gangrene was ruptured and spirochætes were forced into the pleural cavity. Following the formation of a pneumothorax an empyema developed. The pus from the pleural space contained not only *actively motile spirochætæ* but many bacilli and cocci. Cultures of the empyema were sterile on several occasions and it is therefore impossible to state what rôle the organisms other than spirochætes played in the production of the pleural infection. The prompt and marked improvement following the administration of salvarsan lends some support to the assumption that the spirochætes were at least partially responsible for the clinical course of the disease.

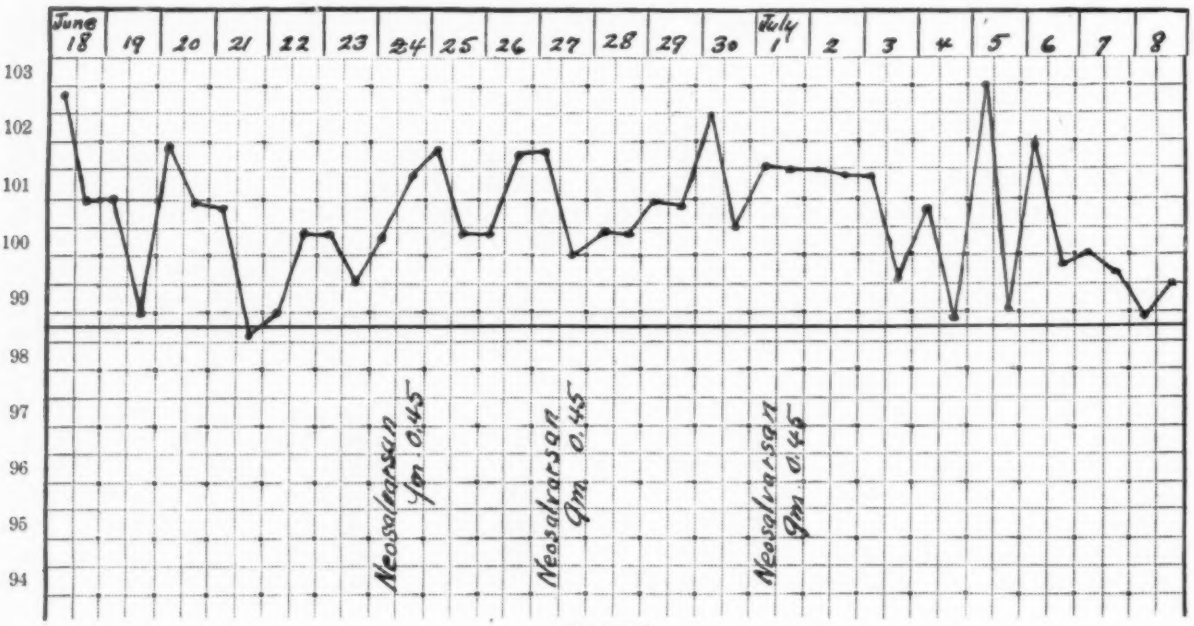


CHART. I.

### GENERAL REMARKS

Spirochætal infections of the lungs were first described by Castellani[2] in Ceylon in 1904. He examined two natives who had had recurring hemoptyses for many months. There were very few physical signs from the lungs and they were not suggestive of pulmonary tuberculosis. Specimens of sputum were consequently examined unstained in order to exclude fungus or fluke infections. He found, however, in each instance numerous actively motile spirochætes. His observations were soon confirmed by Branch[3] in the West Indies and by Waters[4] in India. Cases of bronchospirochætosis have been reported with increasing frequency during the last few years. Clinical descriptions of the disease or reports of cases have come from the Philippines,[5, 6] Switzerland,[7, 8] America,[9, 10, 11] Africa,[12, 13, 14, 15] China,[16] Italy,[17, 18] England,[17, 19] Servia,[20] Belgium,[21, 22, 23] Spain,[24] Peru,[25] Holland,[26] Brazil,[27, 28, 29] Cuba[30] and France.[31, 42] It is apparent, therefore, that the disease, formerly encountered mainly in tropical or subtropical climates, has been observed in many countries located in the temperate zone.

The cases reported from France occurred chiefly during the great war and although many of those affected were Europeans, a large number of them had come into contact with Indo-Chinese and native African troops in whom the disease was relatively frequent. Thus in an epidemic of bronchospirochætosis at Toulon (France) Violle observed that, about a month after the admission of Senegalese and Indo-Chinese

affected with the disease, cases began to appear among troops and laborers indigenous to France, who were, however, patients in the same hospital. It is probable, therefore, that the disease is largely transmitted by direct contact with patients and this opinion is confirmed by a number of laboratory infections reported by Fantham.[4]

The organism, *S. bronchialis*, was first described by Castellani [2] and later more carefully by Castellani and Chalmers [3] and Fantham.[4] It varies from 3$\mu$ to 30$\mu$ in length and from 0.2$\mu$ to 0.6$\mu$ in breadth. The ends are blunt or sharp. There are no flagella. The number of undulations varies from 2 to 8; they are never so small, regular or numerous as those of *S. pallida*. The organism is actively motile. It stains well with the usual aniline dyes and especially well with Fontana's stain for spirochætes. Attempts to cultivate *S. bronchialis* have been uniformly unsuccessful.

The organism is either markedly polymorphous or else more than one type of spirochæte has been observed in the sputum of most of the reported cases. Indeed the case reported by McFie [5] is unique in that all the organisms observed were uniform in appearance. Fantham,[4] however, concluded from a very careful study of *S. bronchialis* and of the mouth spirochætes that the former, not normally present in the buccal cavity, is a distinct species although markedly polymorphous. He asserts that he has seen coccoid bodies, which he believes represent a resting stage of the organism from which new spirochætes are formed.

The relation of the spirochæte of Castellani to the spirochæte of Vincent is, at the moment, a matter of considerable doubt. Spirochætes together with fusiform bacilli have been found in a number of cases,[5, 6] clinically indistinguishable from instances of Castellani's bronchospirochætosis. In far the greater number of reported cases however no fusiform bacilli have been observed, although they have been sought with some care. It is possible, of course, that both organisms may produce very similar clinical pictures when they succeed in producing lung infections, but that by no means proves the contention of Delamare [6] that the two spirochætes are identical. The problem, however, must wait for a solution until better methods of differentiating and identifying spirochætes have been devised.

Attempts to reproduce the disease in animals have met with little success. Chalmers and O'Farrel [7] by intratracheal injections into a monkey of heavily infected sputa succeeded in producing an acute febrile pulmonary infection of short duration and mild course. The sputa of the animal contained many spirochætes. The results of Delamare,[6] and those of Loygue, Bonnet and Pyre,[8] using other animals, were negative or equivocal.

The recent literature [4, 5] contains excellent descriptions of the clinical characteristics of bronchospirochætosis but it may be advantageous at this time to mention briefly a few important clinical facts.

The acute type begins generally with fever, malaise, headache, pain in the chest and cough. The affection at this stage is indistinguishable by physical signs, symptomatology and X-ray examination from a common acute bronchitis. Soon, however, the sputa become blood-streaked and not uncommonly frank hemoptyses occur. The breath may have a peculiar fœtid odor as emphasized by Nolf,[9] and the disease may simulate very closely pulmonary gangrene. Spirochætes are usually abundant in the expectorations by the time blood has made its appearance. After a few days, or rarely a few weeks, the cough and fever subside and the symptoms gradually disappear in the milder cases. In others, however, improvement occurs only after the institution of arsenical therapy.

The chronic type of the disease may follow an acute attack or may begin insidiously. The patient as a rule consults a physician on account of recurring bloody expectoration. Occasionally attacks of fever with some asthenia and slight secondary anæmia alternate with periods of comparative freedom from symptoms. The symptomatology, in such instances, resembles closely that observed in pulmonary tuberculosis, lung fluke infections or certain mycotic infections, and a correct diagnosis is reached only after a careful study of the sputa has demonstrated the presence of spirochætes.

Between the acute and the chronic types many intermediate forms of the disease have been encountered. These may either clear up after several months or may go on into the chronic "pseudo-tuberculous" type (Castellani) of the disease.

Spirochætal infection of the bronchi in a few instances has been combined with certain other chronic pulmonary diseases. Thus Castellani [1] found spirochætes in the expectoration of a patient with a mycotic pulmonary infection, and Branch [3] found the same organisms in the sputum of a tuberculous patient. Recently Sinclair [4] in the Hawaiian Islands found spirochætes usually associated with fuso-bacilli in the sputa of many tuberculous patients who had had hemoptyses. His results, while of interest, have not been confirmed nor correlated with previous observations as yet.

*Treatment.*—The experience of most observers has proved that salvarsan or neosalvarsan in moderate doses promptly and effectively relieves symptoms and brings about a complete cure. Iodides in large doses have also been of distinct value. In many acute cases, moreover, spontaneous recovery has been noted.

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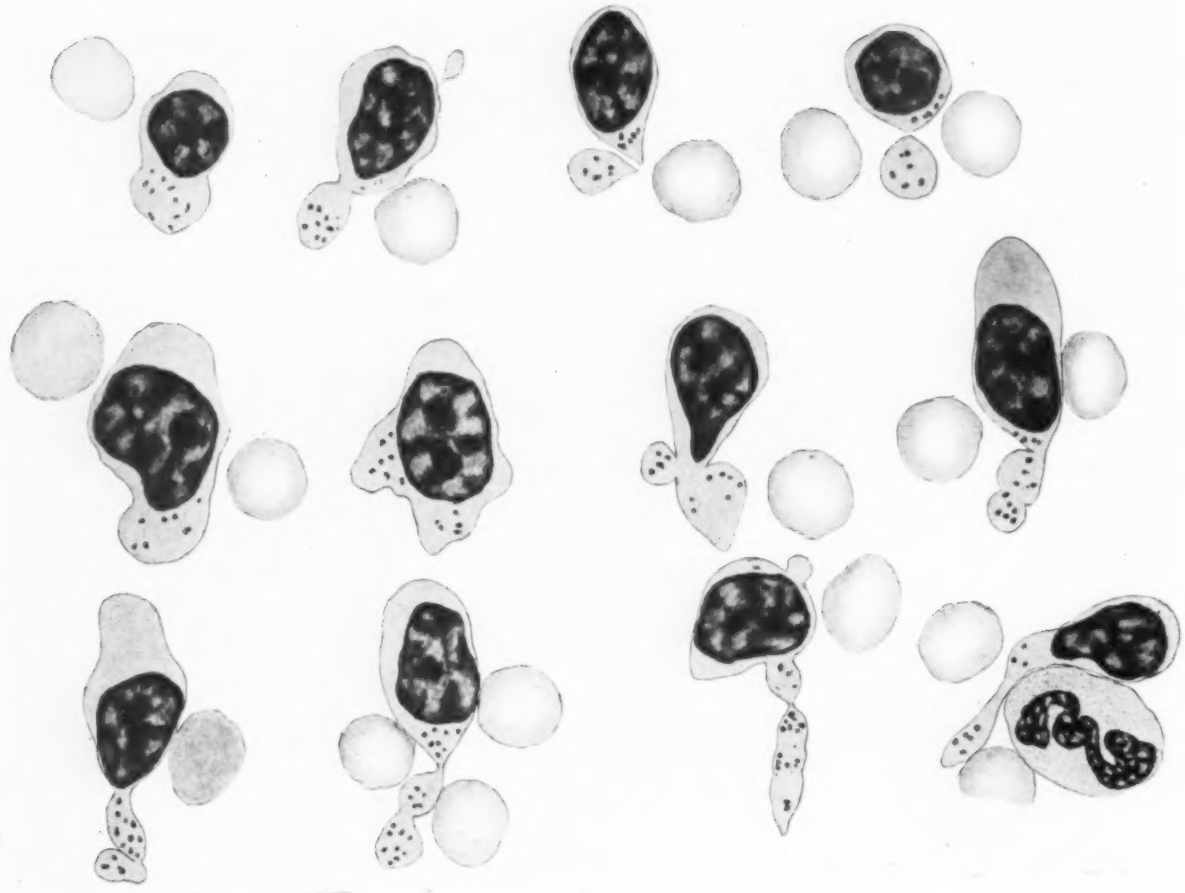

FIG. 1.

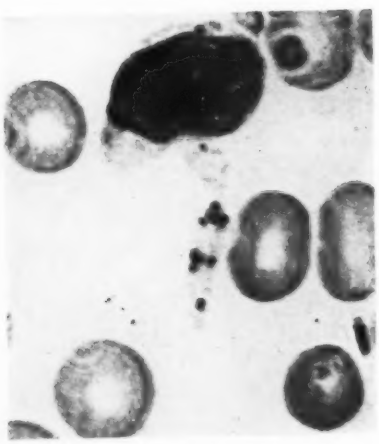

FIG. 2.

# VICARIOUS BLOOD-PLATELET FORMATION

By C. H. BUNTING

*(From the Pathological Laboratory of the University of Wisconsin)*

It is not my intent in this paper to enter at length into a discussion of blood-platelet formation, but to place on record an observation of unusual compensatory or vicarious formation of bodies, analogous, at least, to the normal blood-platelets. Wright's discovery that the normal platelets are formed by the segmentation of pseudopodia projected from the megalokaryocytes of the bone-marrow, seems, in this country, to have had almost unquestioned acceptance as a fact, demonstrated. That in some quarters it is regarded as an unproved theory is shown by the recent writings of certain Italian authors, particularly of Pianese, who does not accept the theory, and of Perroncito, who finds from his investigations no evidence for or against the theory.

I do not wish to reopen the general question further than to say that all the evidence I have been able to obtain from clinical, pathological, and experimental observations, published and unpublished, confirms the findings of Wright for the origin of the normal platelets. The comparative frequence of incompletely segmented pseudopodia and of undivided protoplasmic masses of platelet character in the blood, especially in such conditions as Hodgkin's disease, as emphasized by the author, and in chronic myelocytic (spleno-myelogenous) leukæmia, indicates at once the mode of formation of platelets, and also that the source of the pseudopodia is a cell of greater protoplasmic content than any cell ordinarily found in the blood stream.

That other cells may contribute bodies having the value of platelets, when a platelet-need is established, has been demonstrated by W. H. Brown. He has shown that in the rabbit, after destruction of the megalokaryocytes, certain large multinuclear endothelial cells of the bone-marrow and also the so-called "transitional" cells of the circulating blood may project pseudopodia which segment into platelets. From these experiments he concludes that normally, also, the last-named cells may contribute platelets to the circulating blood, but that the majority of the circulating platelets are derived from the megalokaryocytes.

I have expressed the opinion that the blood-platelets normally do not form a heterogeneous collection of cell fragments but represent a single type of structure as shown by their characteristic staining with Wright's stain. In the examination of literally hundreds of blood-smears from man and animals, I have found no evidence contrary to this opinion and until recently no evidence of any other origin of platelets, if one may except the suggestion offered by a very occasional pseudopodial projection from a transitional cell. These have been so infrequent and usually so small that there has always been doubt as to whether they were genuine or artefacts created in making the spread. However, in a study of the blood of influenza patients of the 1920 epidemic, I have encountered what appears to me indubitable evidence of the compensatory formation of platelets or platelet-like bodies from leukocytes of the circulating blood. I speak of this as a "compensatory formation" for the reason that in influenza there is apparently a sharp inhibition of bone-marrow activity with a marked fall in the number of circulating platelets as one of the results. In blood-smears from early cases, platelets are very few. Agglutinated masses are almost lacking in the smears, and only scattered, isolated platelets are seen. These observations are borne out by the published counts of platelets in influenza by Kinsella and Broun.

The blood of one such case, with the characteristic leukopenia and with extreme reduction in number of platelets, offered a picture, unique in the author's experience. Practically every large lymphocyte in the smear showed some stage in the formation of pseudopodia or platelets. It is realized that in using the term, "large lymphocyte," confusion will be created unless the term is defined. By the term is meant not a member of the large mononuclear-transitional group, nor the pathological large lymphocyte (lymphoblast), nor the intermediate-sized lymphocyte occurring in lymph-gland stimulation, but a cell, common in normal blood-smears, which is apparently a mature form of the small lymphocyte. At least, it is a cell with a nucleus the size of that of a small lymphocyte, but with more protoplasm, which has an acidophilic staining-tendency and contains a few coarse, often rod-shaped, azurophilic granules.

In the smear in question, some of these cells showed merely the collection of the granules about a point in the periphery of the cell; others, a slight protrusion of this part of the protoplasm; others showed the cutting-off of the granule-containing mass, while still others showed the formation of definite pseudopodia of considerable length with grouping of the granules as in platelets and with beginning constriction of the process evident. A reference to the camera lucida drawings in Fig. 1 and to the photograph of a single cell in Fig. 2, may possibly give a better idea of the nature of these changes than can be obtained from a verbal description.

It was also noted in the smears that these lymphocytes had apparently acquired an increased adhesiveness over that normally seen, and in this case, a condition not shown by the other forms of leukocytes. Careful study of the preparations, however, eliminated from the author's mind the possibility that this adhesiveness was responsible for the production of the pseudopodia as artefacts. The clumping of the granules, the beginning constriction of the pseudopodia, the varied direction of extension of the processes, the absence of signs of stress in cells close by, all indicated that here one was dealing with the production of platelet-like bodies, differing slightly morpho-

logically but probably possessing the same functional value as indicated by this very adhesiveness.

A similar process was noted in the blood of several other influenza cases, but in no case was there an approach to the extensiveness of the process, noted in the case described.

The drawings in Fig. 1 were made by the author and his thanks are due Dr. V. C. Jacobson for the photograph in Fig. 2.

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# THE MEASUREMENTS OF INTRACRANIAL PRESSURE CHANGES IN AN EPILEPTIC AND ITS EXPERIMENTAL VARIATIONS

By Franklin G. Ebaugh and Geo. S. Stevenson

*(From the Henry Phipps Psychiatric Clinic, The Johns Hopkins Hospital, Baltimore, Md.)*

This study was planned after a series of observations of the changes in intracranial pressure in an epileptic had been made, at the suggestion of Dr. Meyer. These changes in intracranial pressure were first observed through an area of bone defect without the use of any recording device, a rise of pressure being noted to precede convulsive seizures, and the duration of increased pressure after attacks being timed and recorded.

This area of bone defect in our patient suggested an opportunity not only for measuring variations in intracranial pressure, but also for measuring changes due to the administration of solutions of various concentrations. Furthermore, working on a human subject provided an opportunity for connecting the experimental data concerning changes in brain volume in animals [1, 2] with changes in intracranial tension in man. Since no anesthetics were necessary this factor is eliminated from our results.

Weed and McKibben found in experimenting on anesthetized animals that the intravenous administration of solutions of various concentrations gave an increase or decrease in brain volume according as they were hypotonic or hypertonic, respectively.

Our patient, B. H., is 33 years old, an electrical engineer of considerable ability. The onset of his present illness dates from 1913, when he complained that he frequently had difficulty in talking and transitory periods of haziness of consciousness. These attacks were all preceded by a perception of a definite, peculiar odor, which he described as sweetish but not unpleasant. He grew much worse gradually, and in the early part of 1914, while at work, he had his first spell of unconsciousness. This attack was instantaneous, and although he he thinks he noticed a peculiar smell preceding it, he is not sure. He had an amnesia for this attack, and fell on his face with injury. Soon after this attack he accepted a position in an important engineering project. During the next three months, he felt much better; he had frequent petit mal seizures, but no convulsions. He worked very hard and was confined much of the day. In May, 1914, his unconscious spells and convulsions became more frequent and he was forced to give up his position. He usually had an olfactory aura before each attack, which began with a cry, and lasted from 5 to 20 minutes, and usually included tonic and clonic convulsions. These convulsions were not accompanied by salivation and biting of his tongue. There is no history of incontinence. He suffered from amnesia before the attacks and at times had difficulty in finding the correct words while talking. He returned to the United States, and in June, 1914, a left exploratory craniotomy was performed by Dr. Dandy, of The Johns Hopkins Hospital. The left Rolandic area was exposed and a subarachnoid cyst was evacuated. A definite thickening of the pia arachnoid was present. He showed little improvement following the operation. During 1915 and 1916, he occasionally had convulsions. He continued to have difficulty in finding the correct words in talking. He took up Christian Science and at times felt much encouraged, and returned to work for short intervals. He frequently injured himself during attacks, occasionally he bit his tongue; no frothing nor incontinence was observed.

He was admitted again to the surgical service, April, 1917. At this time his difficulty in speech was thought to suggest a motor type of aphasia, and he gave as his complaint difficulty in talking, thinking and hearing. Convulsions had usually occurred at the rate of from one to two per month. They were not followed by headache; he usually felt relieved afterwards and was able to return to work. In May, 1917, Dr. Heuer performed a left craniotomy and evacuated a subarachnoid cyst. One week later he had a generalized convulsion in which he struck his head. No aura preceded this attack and it was followed by general weakness and numbness of the right side. He was discharged with no further treatment.

There was no change in the character of the convulsions after the second operation. The patient attempted clerical and mathematical work but found himself handicapped by difficulty in thinking and by periods of forgetfulness and stupidity. A sub-temporal decompression with opening of the dura in June, 1918, brought no improvement. The attacks had increased in number to an average of from one to three per week at the time of admission to the Henry Phipps Psychiatric Clinic, November 20, 1919. During the first month in the hospital the patient had 10 generalized convulsions. He could tell of no definite aura, but on several occasions he said that

he had a funny feeling in his head. He gave the characteristic initial cry followed by general tonic and clonic convulsions, with his mouth open and staring straight ahead. He did not bite his tongue but occasionally received severe injuries through falling. He rarely frothed at the mouth and incontinence rarely occurred. His pupils were fixed to light and frequently he showed a bilateral positive plantar response. The attacks usually were of 5 to 20 minutes' duration and were not followed by periods of sleep. The patient was observed to be less tense and depressed after the attacks. He had frequent petit mal attacks, characterized by momentary loss of consciousness with pallor. There was a definite amnesia with all the attacks. During his stay in the hospital, the patient continued having from 1 to 7 convulsions per month. He averaged from 5 to 10 petit mal attacks each month. He showed an interesting speech difficulty which he explained as follows: "I know what I want to say but I can't think of the right word." On frequent occasions he complained of inability to derive any meaning from what he read. His spelling of test words was definitely faulty; the repetition of given words was slow and inaccurate. He showed a slight retention difficulty in giving the gist of short stories which he had read previously. He showed periods of restlessness during which he complained of feeling depressed. He was unable to describe the events of his illness in sequence, and his statements differed from those given by relatives. The memory defect was usually in proportion to his difficulty in expressing himself correctly. In the main he showed fair retention, grasp of general information and calculation, judgment and insight. The patient was very suggestible and he was enthusiastic over any new attempt to treat him. In our experimental work it was necessary to take into account this suggestibility, so he was not informed of the results we expected, or given any of the facts as to the nature of subsequent work. Any change in treatment resulted in subjective improvement. He was not given bromide treatment, and the attacks did not occur as frequently as at home. Starvation periods seemed to help him somewhat. His general physical status was good.

The neurological examination showed loss of smell in the left nostril. In both eyes the veins were full and tortuous; the margins of the discs were distinct.

Blood examination: R. B. C. 4,800,000. W. B. C. 8000. Hb. 90 per cent. Normal differential count.

Spinal fluid examination: Negative.

Gastro-intestinal series of X-ray pictures proved negative.

Our patient readily cooperated with all experimental work, even after it was explained to him that it would cause much inconvenience on his part.

### Apparatus and Method of Application

The registering device consisted of an inverted tambour covering the area of bone defect, and connected with a manometer or a kymographic outfit.

The tambour was the usual type, being a short cylinder (Fig. 1) 5 cm. in diameter and varying in length with the contour of the open end from 1 to 1.5 cm. In order to secure a good application of the tambour to the margin of bone around the defect, a plaster negative of this region of his head was made in the Orthopedic Department. From this a clay positive was made and used as a model. The edge of the tambour over which the rubber was drawn was made to fit the contour of this model. At a point 6.5 mm. from the closed end of the tambour a flange was soldered on, in order to secure the dam, and between this and the closed end a rubber band was cemented around the tambour, so that the cords binding the dam might have a soft surface in which to burrow, and make the junction air-tight. From the flat surface of the tambour—the closed end—there were two outlet "L" tubes directed oppositely, and at about 45° to these brass wire eyes projected from the tambour, for the attachment of the strap with which the instrument was held to the patient's head. This strap consisted of 3 cm. wide web, such as is used in head extensions, sewed to the eyes on the tambour and buckling over the opposite (right) temple. The rubber dam used for the head tambour and for the recording tambour was of light weight. A piece of this was also put between the head tambour and the patient's scalp, in order to prevent the rotting of the tambour dam.

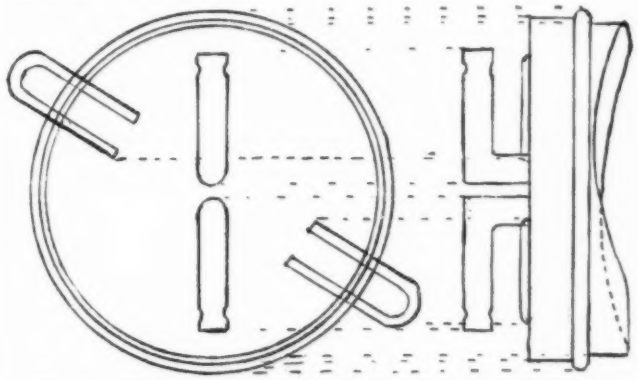

FIG. 1.—Diagram of tambour applied to the patient's head.

The manometer was a U-tube of 2.5 mm. caliber enclosed in a wooden case so as to be portable, and registering up to 150 mm. water of pressure. One end of this U-tube was connected to an outlet tube of the head tambour. In order to prevent kinking the outlet tube pointing downward was used. On the other end of the U-tube was a short piece of rubber with a screw clamp on it, to prevent fluctuations of the manometer when not being read, since certain activities of the patient, as coughing, would cause the manometer to overflow. Water was used as the displaced column in the manometer. Connections were made with red rubber tubing and tightened with a ring of copper wire.

From the other outlet tube of the head tambour was a free rubber tube of sufficient length to allow the patient to move in bed. When the manometer was in use, this was clamped off close to the head tambour. When the kymographic recorder was used, the manometer was clamped off and this free tube was attached to the recording tambour on which the lever rested which marked on the kymographic drum.

Owing to the fact that the kymographic attachment considerably increased the air space of the system, at the usual pressure was not very sensitive, and offered another opportunity for leakage of air, this was clamped off when manometer readings were being taken; and since manometer readings at the pressure required for kymographic record were very low, the manometer was clamped off when tracings were obtained.

As a result, perhaps, of the permeability of the rubber, there was a fall of pressure in the system during 12 hours of usually about 10 mm. when set up off the patient's head, at the pressure existing when applied, *i. e.*, 70 to 80 mm. Immersion in water did not disclose any other cause for this escape of air.

In order to calibrate the tension of the rubber dam for comparison when changes were made, the manometer head tambour system was closed at atmospheric pressure, and the effects of various weights, ranging from 5 to 5000 gm., put upon the dam were recorded. Subsequently it was found that practically no difference in tension existed after change of the dam. As no stretching was needed this was expected.

The bone defect of the patient is situated just above the left temple, giving an excellent opportunity for a firm fixation of the tambour. Since the dura had been opened the area of bone defect presented a fair degree of elasticity, enabling us to follow pressure changes at a close range. The method giving the most constant results was to lay the protective rubber over the defect, apply the tambour so that its contour fitted the head, have the patient report on the comfort of the contact and, if satisfactory, hold it in place. The posterior strap was then passed under the occipital protuberance, above the right ear, meeting the anterior strap at the temple over which it was buckled. The anterior strap passed over the forehead just below the hair line. In buckling it was important to hold the straps in position to prevent slipping, and to judge the tightness by the force used and the wrinkling of skin beneath the buckle (Fig. 2). The feelings of the patient were found to be a good indication of a proper application, and after getting used to it he assisted considerably in this. Although he had some discomfort from the head gear at first, he was soon able to sleep with it on. With a good contact the instrument stayed in place well. When pressure readings were desired, before application the head tambour was disconnected from the kymograph system, the free tube was opened to permit the manometer to register zero and then clamped off. The instrument was applied with the patient in a sitting position, his head turned with the defect pointing up, readings being taken from the manometer with the patient sitting erect and also while he was lying in the lumbar puncture position. These readings represent of themselves no absolute values but are arbitrary along with the original zero pressure. Since the manometer readings vary considerably with change of posture these two postures were adopted.

In order to determine the error of application of the head tambour, ten successive applications were made. These gave 60, 55, 55, 65, 62.5, 52.5, 62.5, 55, 60, 55, averaging 58.3, with a maximum deviation of less than 7.5 mm. and a maximum variation of 12.5 mm. On other trials even better results were obtained. In applying it for experimental work three trials were made, and, if satisfactorily close, a subsequent application registering the average of the three was used. Faulty applications showed an ascent of pressure readings until a self-adjustment took place. A proper application showed no such change.

Comparison of the arbitrary readings with actual pressure was made by applying the apparatus, putting the patient in the lumbar puncture position, taking readings over a short period, and then performing a lumbar puncture and taking readings from a gauge attached to the needle at the same time as from the manometer. The spinal fluid was gradually run off to zero and then returned.

The results of simultaneous readings of spinal fluid pressure and pressure registered through the head tambour are as follows:

| | Head manometer | Spinal fluid manometer |
|---|---|---|
| Applied to head | 85 mm. | |
| Punctured (escape of about 2 c. c. of fluid) | 80 | |
| Cock opened | 70 | 110 |
| | 70 | 95 |
| | 65 | 95 |
| | 65 | 90 |
| | 67.5 | 70 |
| | 62.5 | 60 |
| | 60 | 45 |
| | 55 | 45 |
| | 55 | 0 |
| Fluid returned | 52.5 | |
| | 60 | 105 |

The original reading of 85 dropped to 80 as some fluid was lost in connecting the gauge, and to 70 as the gauge filled up. At zero spinal fluid pressure it was 55 but fell to 52.5 as the fluid was returned. This probably represents the actual zero point for the point in lumbar puncture position and was caused by delay in the displacementof the fluid. The return to 105 in spite of the 4 c. c. being retained for examination suggests either a delay in redistribution or else a rather rapid resecretion of fluid. These readings are of great significance, since it is obvious that the changes in pressure in the recording system applied to the area of bone defect in the head represent only relatively the changes in absolute pressure in the cerebro-spinal fluid. Such changes as were recorded by the head manometer may, however, be considered as indicative of corresponding changes in the cerebro-spinal pressure. A fall of 10 mm. in the head tambour is equivalent to one of 30 mm. in the cerebro-spinal pressure.

### Intracranial Pressure Changes and Kymographic Tracings

Investigations were directed towards:

(1) A study of gross changes in intracranial tension. (2) A study of manometer readings. (3) A study of kymographic tracings.

During April and May, gross observations on changes in the depth of the area of bone defect revealed filling or increased

pressure preceding, during and following nine out of ten convulsions. It is probable that our percentage would be 100, if the other attack recorded had been examined for pressure changes. On other occasions a definite relation was noted between this increase in pressure and the patient's general condition, since he frequently complained of feeling as if an attack were coming on when the filling was marked in the area of bone defect. Often he appeared tense and depressed during these intervals with a general improvement in his mood following a return to normal pressure. Pressure changes were also noted before petit mal seizures. These were less pronounced than during grand mal attacks. This was especially noticeable on April 19, when the patient had three petit mal attacks. On this day transient increases in pressure were recorded on five different occasions.

It is interesting to note that this increase in intracranial pressure is associated with increase in blood pressure.[3] Twice we were fortunate enough to obtain readings just before the onset of a generalized convulsion. These readings averaged 20 to 30 mm. of mercury higher than control readings. On several occasions the tension appeared marked, with bulging in the middle of the bone defect simulating herniation. The patient complained of tinnitus and headache. Although the eyegrounds were examined, no edema or evidences of increased intracranial pressure were observed when he made these complaints. On rare occasions he complained of a peculiar odor and taste, but on examination he named the test solutions correctly.

The accompanying chart shows the time relations of increased tension. Only readings observed before experimental variations in intracranial tension were obtained are given.

| Date | Attack | Duration of increased pressure |
|---|---|---|
| March 28 | Grand mal | 6 minutes. |
| March 29 | Grand mal | 7 minutes. |
| April 1 | Grand mal | 4½ minutes. |
| April 14 | Grand mal | Increased—but not timed. |
| April 19 | 3 petit mal | Intervals of 12 minutes.<br>Intervals of 22 minutes.<br>Intervals of 5 minutes. |
| April 21 | Petit mal | One hour before attack. |
| May 3 | Grand mal | 45 minutes. |
| May 7 | No attack observed.<br>Complained of feeling badly. | 2 hours and 45 minutes. |
| May 10 | Grand mal | Intermittently for next 3 days. |
| May 13 | Petit mal | Increased—but not timed. |
| May 21 | Depressed | Increased—but not timed. |
| May 23 | Grand mal | 3 minutes, and intermittently for next two days. |

When the manometer was used, the instrument was applied in the usual way. The patient was allowed to go about the ward in his usual activities, sitting down for readings every 15 minutes. Being an engineer, he was able to do most of the recording himself. Occasional readings were taken with the patient in the lumbar puncture position. The readings were continued usually over a period of eight hours and were recorded on cross-section paper. From these data several things could be noted; first, the relation of the two positions; secondly, the daily and hourly variations in the individual curves, and third, a study of a composite curve, averaged from all those obtained.

The sitting posture was found to bear a definite relation to the lumbar puncture posture. Most of the readings, when the patient was seated, fell within 45 to 85 mm. of water. The pressures in the lumbar puncture posture were grouped for each 5 mm. pressure, in the sitting posture, within the 45-85 limits, and these pressures were averaged for each group. It was thus found that the differences in the two postures at different pressures were practically the same, ranging from 35 to 40 mm. and averaging 37.5. Beyond these limits our readings were fewer, and no constant relation could be made out.

A study of the curves themselves shows very little. There is a suggestion that activity tended to raise the pressure. On one occasion there was a gradual fall in pressure of 10 below the average, while the patient was eating a meal, with a gradual rise afterwards to 10 above. On another occasion after a 5½ hour variation of only 5, on his going to the dental clinic for a filling it rose 10 mm. above his previous maximum and then fell 25 mm. There was a constant tendency towards a fall at the end of the day. We have here a set of facts which we feel are worth recording, but which we have not attempted to control or interpret. The finding of a rhythmic fluctuation in spinal fluid pressure, through kymographic tracings to be discussed further on, would lead us to expect periods of fluctuation and periods of stability in manometer readings.

A study of the normal composite curve, made from an average of all the normal curves, shows very little outside of its evenness, and a slight fall toward the end of the period of observation. No importance can be placed upon the latter feature, since, as we have previously noted, the rubber is slightly permeable, and liable to show the same fall when under the same pressure off the patient's head.

Although our manometer readings, relative to epilepsy itself, are too isolated to warrant generalizations, it is interesting to note that, on one occasion when the patient was dazed and speech was difficult, the intracranial pressure was increased over a period of 4½ hours, during which he had three petit mal attacks. On another occasion he had seven grand mal attacks in 48 hours, followed by a period of four days during which he was in bed, dazed. During this whole period the bone defect showed bulging. The manometer on these days read 120, 120, 120, 125, respectively, with much increased pulse excursions. On the fifth day it read 110, and fell very gradually to 70 as the patient got up and went about. After 1¾ hours in bed it had again risen to 105 and fell gradually after he got up again. These manometer readings represent far greater intracranial pressure changes, as has been explained previously. The slow return of pressure to normal limits after lying may in this state be of significance, since ordinarily it required practically no time to adjust itself.

By resorting to kymographic recording, we were able to detect, from second to second, changes which could not be made

out otherwise. There were thus revealed three types of waves (Figs. 3 and 4): First, a normal arterial pressure tracing; second, a normal respiratory variation, and, third, a wave definitely but irregularly rhythmic, averaging about 90 seconds each, but varying greatly in time. These last waves were of two types. First: There were groups of nicely rounded shallow waves, a little more frequent than the average and occurring in pure culture (Fig. 5). The second type showed a slow rise, suddenly forming a peak and then a sudden fall (Fig. 6). These likewise occurred in groups. It is of interest to compare both these types with some of Carlson's records of gastric contractions,[4] where identical waves are found. These waves not only occurred in groups but there were intervening quiescent periods (Fig. 4). They were first noted at night while he was asleep, six hours after his last meal. They were noticed most clearly after a period of starvation especially those of the second type. Synchronous gastric and intracranial pressure tracings (Fig. 7) show a relation between changes in the two (Fig. 7). This is probably on a vasomotor basis, as suggested by Carlson. Evidence points to an association here.

There were certain definite activity curves of a constant form. Clearing of the throat or coughing always produced a sudden rise and fall, followed by a slight rise and gradual fall. A prolonged increase of intrathoracic pressure produced a high plateau.

The act of urination showed an initial and terminal rise usually with rises in the midst of the act. The straining accounts for the rises. Deep breathing merely accentuated the respiratory waves. Snoring did this even more. Holding the breath after a deep inspiration shows a very typical curve (Fig. 8), for example, a rise consuming 5 seconds followed shortly by a fall consuming 4 seconds, then a rise during 6 seconds to a higher level and a slight fall during 4 seconds. After running level for 30 seconds longer a rise and gradual transition into extreme fluctuations associated with respiratory movements of the chest occurred and lasted till the end of 90 seconds, when the patient took a breath; a prompt fall followed, a sudden rise again and a gradual fall during the next 15 seconds. When respiration was stopped at different phases, a typical curve resulted. When stopped at the end of expiration it was less shallow, and more irregular than at the end of inspiration. Even the act of swallowing produced a typical curve—a sharp peak upward with a shorter one downward.

On two occasions we were able to record petit mal attacks. These records were similar in their form, the typical feature being a rapid rise associated with an increase in amplitude, which we were unable to duplicate experimentally. One of these (Fig. 9) occurred after a 7-minute period of study, and persisted for 3½ minutes. The rise with increased amplitude and fall to normal level lasted over one minute. During this time the patient lay still and stared ahead. During the next 2½ minutes he gave responses which he could not remember later. He then became fully conscious, but for 3 minutes there were irregularity and increased amplitude. On a third record taken when the patient felt as if he had aborted an attack there was a sharp rise and fall, covering 5 seconds, followed by an increased amplitude and irregularity. There was no apparent loss of consciousness.

Robbins[5] has recently demonstrated similar changes in intracranial pressure during various activities, such as sniffing, stammering, etc., which he found were always associated with an increase in brain volume. He found also that shock, fear of stammering and emotions of every kind caused an increase in brain volume, accompained by increased size of pulse. Angelo Mosso[6] has also shown the effects of the emotions in producing cerebral vascular changes. He investigated the movements of the blood vessels and bladder movements with the plethysmograph and found waves coinciding with the respiratory movements. When he investigated blood pressure changes he obtained fluctuations as described by Traube. The respiratory curves exhibited periods of greater or less activity depending on the activities of the patient. Leonard Hill[7] obtained similar curves and demonstrated the dependence of intracranial pressure on the general arterial and venous pressure.

### Changes in Pressure Produced by Solutions of Various Concentrations

The object of this study was to determine if we could establish a link between the experimental data concerning change in brain volume in animals and man. We desired to confirm Weed and McKibben's[1, 2] work, which dealt with changes in brain volume in cats. We were fortunate in having a trephine opening present and that no anæsthesia was used. We were fortunate, also, in that our patient co-operated from the very beginning of our work, and we were able to obtain data of subjective changes along with objective manifestations. We could take readings over long periods of time, and follow variations in intracranial pressure under more ideal conditions than would be possible with animals. During all our work, however, nothing of an experimental nature which would result in any marked change in the patient's general condition was done. For this reason we did not attempt to control our manometer readings, obtained over the area of bone defect, by repeated lumbar punctures, although this would have enabled us to follow the pressure changes in the cerebrospinal fluid at a closer range. We have relied entirely on our previous standardization of the relation of intraspinal pressure to our manometer readings; thus we have obtained only relative cerebro-spinal fluid pressure readings. Pressure readings taken over the area of bone defect, owing to the resistance of the skin and dura, represent far greater changes in intracranial pressure than can be recorded by our tambour.

The changes produced in intracranial pressure were observed by simple observation of the bulging as well as through manometer readings obtained by the method previously described. It is interesting that these changes were frequently commented upon by the patient himself, who used them as a gauge for his activities. When he felt badly he learned to feel his head, and if he noted filling in the area of bone defect he usually remained in bed or in a protected position. On

these occasions he frequently gave typical complaints, as follows: He felt as if an attack were coming on; at times he noticed a peculiar odor; his head felt full; he complained of tinnitus; feeling shaky all over, etc. When the area of bone defect was depressed, he was usually brighter, more alert, spending his time working at various mathematical problems and reading an elementary astronomy book. These findings suggested that future therapeutic applications could be made, especially if we could obtain constant changes in intracranial pressure by giving hypertonic and hypotonic solutions.

In choosing our solutions, we followed the lead of Weed in using a hypertonic Ringer's of the following formula:

| | |
|---|---|
| Sodium chloride | 18 gms. |
| Potassium chloride | .085 gm. |
| Calcium chloride | .50 gm. |
| Water | 100 c. c. |

We also used a 30 per cent glucose solution. We used tap-water for our hypotonic solution. After first determining our patient's capacity, we were surprised at the beginning that he could take from 4000-5000 c. c. of water in the course of 1¼ hours, and chose 4000 as our unit. The patient would drink 1000 c. c. at the beginning, 200 c. c. every five minutes up to 4000 c. c., making an interval of 1¼ hours. We used normal salt as our isotonic solution, giving this as a control in the same amounts as for hypertonic and hypotonic solutions. All of these solutions were given by mouth with the exception of the hypertonic glucose, which was administered intravenously. In the case of hypertonic solutions, they were all administered in quantities of 200 c. c.

We followed the same method for obtaining our readings as for actual measurements of changes in pressure commented upon previously. Our patient was allowed to go about the ward, as usual, and no solutions were given until after manometer readings had been taken for an hour or more, demonstrating that no leaking had occurred and that the application of the tambour to his head was satisfactory.

*Hypertonic Solutions.*—We found that following the oral administration of hypertonic Ringer's (19 per cent) a constant fall of intracranial pressure resulted. This fall usually began within 15 minutes and continued for an average of 1¾ hours. There was a fall from 15 to 20 mm. of water and this was followed in all experiments by a subsequent rise of pressure over a period averaging 3½ hours, when the initial pressure was reached. Later this rise of pressure exceeded the initial pressure. These changes were found to be a constant occurrence, as is demonstrated in Fig. 10 by the composite curves of seven experiments and also of a typical curve. This fall of pressure represented a far greater decrease in intracranial pressure owing to the resistance and inelasticity of the skin over the area of bone defect.

After the administration of the solution, the patient complained of intense burning in his throat and epigastrium usually of 2-4 hours duration. A constant catharsis resulted. Pallor was always present and the patient complained frequently of weakness. On several occasions he gave his characteristic complaint of feeling shaky, of being confused at times, of finding it hard to express himself. He did not complain when the terminal rise of pressure occurred. For the practical therapeutic application of this method for the transient reduction of pressure, however, this terminal rise of pressure must be taken into consideration, as well as the unpleasant subjective symptoms.

We were unable to try out other hypertonic salts on an extensive scale. On one occasion when high pressure was noted in the area of bone defect, we obtained striking results after the administration of one and a half ounces of sodium

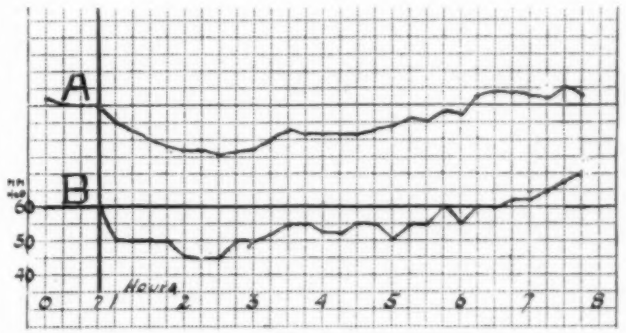


FIG. 10.—*A*, composite, and *B*, typical curve of intracranial pressure changes produced by the oral administration of 200 c. c. of 19 per cent Ringer's solution.

sulphate given in 200 c. c. water. An instantaneous fall of pressure resulted, reaching a maximum of 50 mm. pressure in the next hour (Fig. 13). This fall most likely means a fall to zero pressure in the cerebro-spinal system. There was no subsequent rise in pressure during the course of 9 hours. Of course these changes were accompanied by a marked catharsis, and the dehydration resulting may be an important factor in lowering intracranial pressure.

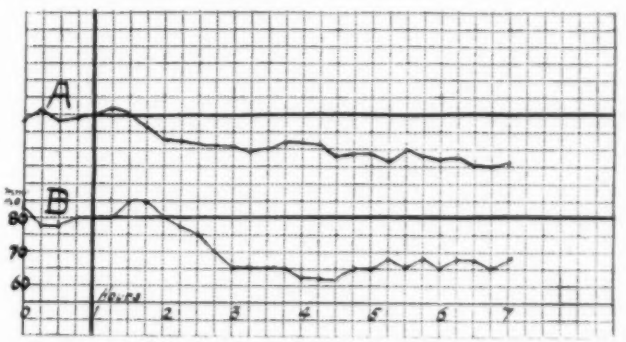


FIG. 11.—*A*, composite, and *B*, typical curve of changes of intracranial pressure, produced by the intravenous injection of 200 c. c. of 30 per cent glucose.

*Hypertonic Glucose.*—In dealing with a solution of glucose, it must be borne in mind that the diffusion time of glucose is three times that of salt and the osmotic pressure is proportionately less.

While the changes resulting from intravenous 30 per cent glucose were not as striking as those from hypertonic Ringer's, the findings were constant and no terminal rise in pressure occurred even after 8¾ hours. This fall in pressure averaged

15 mm. as a maximum (Fig. 11). With hypertonic glucose, the fall in pressure was more gradual and prolonged than in the case of hypertonic Ringer's. There was a fairly constant, transient, initial rise in pressure following the administration of hypertonic glucose.

The patient had no unpleasant subjective symptoms following the intravenous injection of this solution. The time of injection varied between 12 and 20 minutes. A slight flushing of the face always accompanied the injection. There was no subsequent diuresis and the patient gave no evidence of somatic changes except on one occasion when he had a chill one hour after the injection. He complained of intense headache, and of pain in his back and legs. His temperature rose from normal to 101.2°. He had a leukocytosis of 14,260. The urinary examination was negative. This reaction subsided completely in the course of three hours and was the only untoward one he exhibited.

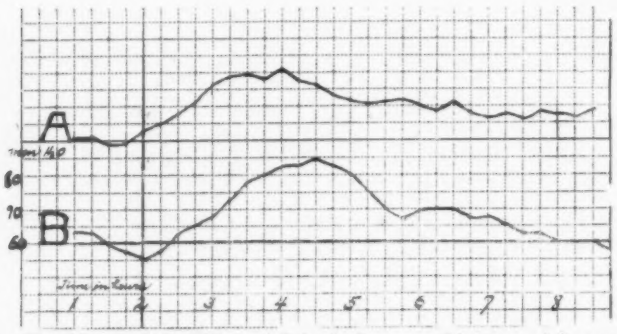


FIG. 12.—*A*, composite, and *B*, typical curves of intracranial pressure changes, produced by the oral administration of water (4000 c. c. in 75 min.).

We feel that the results obtained with hypertonic glucose indicate a definite advantage of the clinical use of this solution over hypertonic Ringer's. A more prolonged fall of pressure resulted without subsequent increase, and the patient had fewer unpleasant symptoms. The use of this substance is rapidly becoming more general and the results are often striking as Haden [8] has shown in his article.

*Hypotonic Solution.*—We obtained an average rise of 20 mm. (water) following the oral administration of 4000 c. c. of tap-water. During the ingestion of the water a gradual rise in pressure resulted and continued for an average of three-quarters of an hour after the last 200 c. c. were taken. This is shown in a composite curve of five experiments along with a typical curve (Fig. 12). This rise in pressure was always followed by a gradual fall to the initial pressure during the course of two hours. On one occasion by forcing water to the limit, 8000 c. c., over a period of six hours, we were able to obtain a uniform maximum of pressure with no fall.

The patient seldom complained while taking the water, although afterwards he complained of fullness and frequent urination. This diuresis was noted to be synchronous with the fall in pressure to the initial reading. When the pressure was at its maximum he gave typical complaints. On all occasions he complained of a feeling of fullness in his head and of intense tinnitus. Frequently he complained of headaches and of feeling as if an attack were coming on. On one occasion an actual grand mal attack resulted after a fairly stationary increase of 20-30 mm. pressure. It is interesting to note that this attack occurred during sleep, and that preceding the drowsiness the patient complained of a terrible headache.

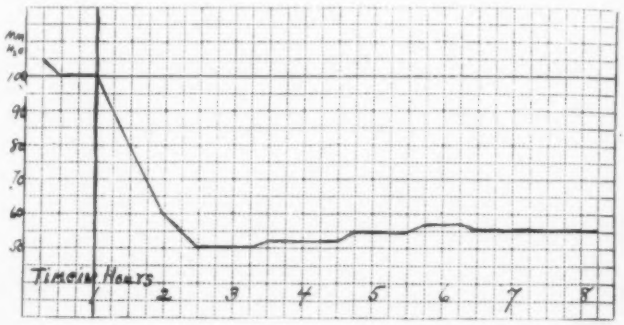


FIG. 13.—Curve obtained after giving hypertonic sodium sulphate showing a drop in pressure of 50 mm. Maintained for an interval of 8 hours.

### CONTROL READINGS

We attempted to control our results by: (1) A series of readings with the patient in his usual activities; (2) isotonic solutions administered in the same quantities as used for hypertonic and hypotonic solutions.

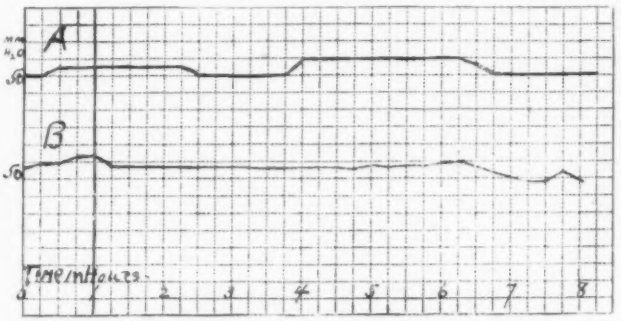


FIG. 14.—*A*, control curve—4000 c. c. of 85 per cent sodium chloride which controls volume of fluid given orally for both hypertonic and hypotonic solutions. Curve shows a maximum variation of 5 mm. pressure. *B*, composite of 8 curves taken with subject in usual activities.

For our normal control a composite of eight readings (Fig. 8) shows a maximum variation of 8 mm. However, this fall occurred late in the day and we have found a similar result from probable permeability of the rubber dam.

In order to control our experiments, in which we used hypertonic Ringer's solutions and hypotonic solutions, we used 4000 c. c. of normal saline solution. This was given by mouth. Our control curve (Fig. 14 *A*) shows a maximum variation of 5 mm. in pressure. Normal saline given orally of the same volume as the hypotonic solution adequately controlled this experiment. Since this is equivalent to 20 times the volume of our hypertonic solutions administered orally it also furnishes a definite control for our experiments with hypertonic solutions.

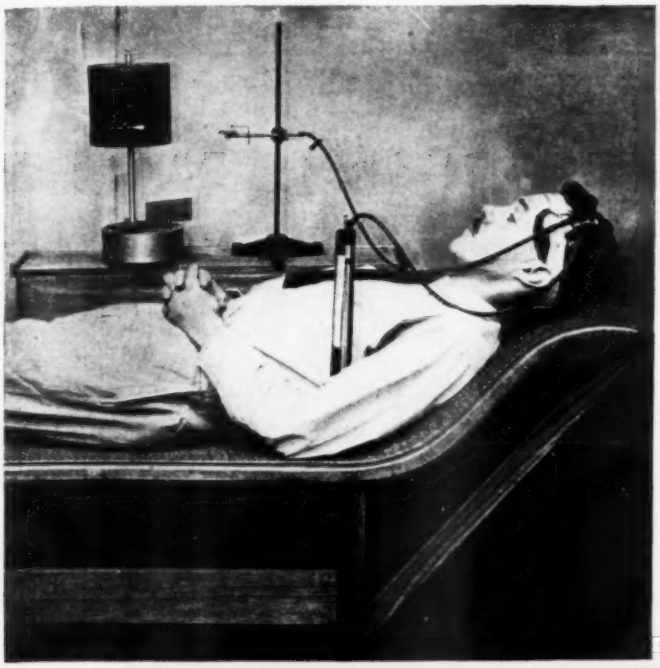

FIG. 2

FIG. 3

FIG. 4

FIG. 5

FIG. 6

FIG. 7

FIG. 8

FIG. 9

SUMMARY

1. Intracranial pressure changes may be measured by the application of an inverted tambour to an area of bone defect. With this recording tambour we were able to observe changes in intracranial pressure, which roughly follow absolute pressure changes in the cerebro-spinal fluid.

2. Rhythmic changes in intracranial pressure of varying types have been recorded.

3. Epileptic attacks are associated with a rise in intracranial pressure and are unaccounted for by activities of the patient. A rise of blood pressure sometimes occurs with the rise of intracranial pressure during the attacks. The patient gives subjective complaints associated with these changes.

4. Petit mal attacks show typical kymographic tracings of pressure changes.

5. Intracranial pressure is lowered by the intravenous and oral administration of hypertonic solutions. The oral administration of 200 c. c. hypertonic Ringer's gives a transient fall of 20 mm. ($H_2O$) with a terminal rise of pressure. From 30 per cent hypertonic glucose given intravenously we found a prolonged fall of pressure averaging 20 mm. after a slight initial rise. These changes observed by our recording system represent far greater changes in the true intracranial pressure. Glucose is more ideal to use for therapeutic purposes.

6. The administration of hypotonic solutions (water) gives a constant increase of intracranial pressure.

7. These changes are adequately controlled by the use of isotonic solutions.

We wish to express our appreciation to Dr. Adolf Meyer, Dr. Lewis Weed, and Dr. Leslie B. Hohman for their valuable suggestions and kindly criticism in carrying out this study, and to the patient for his unusual co-operation and assistance.

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DESCRIPTION OF PLATE

FIG. 2.—Photograph showing the application of the tambour to the patient's head, and the attachments for recording changes in pressure.

FIG. 3.—Tracing showing circulatory and respiratory variations.

FIG. 4.—Waves of third type showing transition to a quiescent period. Obtained during starvation.

FIG. 5.—Waves resembling those of gastric tonus.

FIG. 6.—Waves resembling gastric contractions.

FIG. 7.—Synchronous gastric and intracranial pressure changes showing parallel variations. Moved at *M*.

FIG. 8.—125-second apnœa curve.

FIG. 9.—Tracing obtained during a petit mal attack.

# THE DETERMINATION OF ACETONE IN THE BREATH

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For the past five years, we have been using in this clinic a chemical method of estimating quantitatively the acetone in the breath, determining in this way if acetone bodies are present in the body and roughly in what amounts. We have found this of practical value in many cases, especially in dealing with the following problems:

1. In patients with hyperpnea, when acidosis is recognized or suspected, it is important to know immediately if acetone bodies may not be the cause of the condition. Although analysis of the urine would give the desired information, there is often failure or delay in obtaining a specimen, so that the determination of their presence or absence in the breath affords an important saving of time. The time element is particularly important here, as an acetone body acidosis (except in diabetes) usually responds readily to early treatment by the administration of carbohydrates.

2. In diabetic patients, the determination of acetone in the breath affords a rapid quantitative measurement of the amount present in the body; the determination is useful in diagnosing diabetic coma, and in following the condition of a patient when coma is impending or when changes in diet are being made.

3. In cases in which a patient has been getting little or no food, as in fasting or recurrent vomiting, the determinations of the acetone in the breath act as a guide to the patient's condition.

Quite recently Widmark[1] has shown that acetone passes from the blood to the alveolar air by a process of diffusion, and that the acetone content of the blood and of the alveolar air are proportional. This gives the determination of the acetone in the breath a firmer footing, as it means that the acetone in the breath is a rough index of the acetone in the blood.

[1] Biochem. Jour., 1920, xiv, 379.

The method we have used has been based on that of Scott-Wilson.[2] Hubbard[3] has used the Scott-Wilson reagent to determine the acetone excretion through the lungs. Hubbard's method is quite lengthy and enters into refinements in that interfering substances such as primary alcohols, aldehydes, etc., are removed. For clinical purposes, however, this is not at all necessary.

The air for the determination is collected in a rubber bag of 1000 c. c. capacity when full. A football bladder should prove satisfactory. The air may be collected in various ways. When possible, it is most satisfactory for the patient to blow up the bag as one does a toy balloon. With babies or unconscious patients, a mask and valves may be used, or the patient may breathe back and forth several times from a bag containing air, as in the Plesch method of obtaining the alveolar air. The results obtained when using alveolar air are higher approximately by twice those when valves are used; but this is unimportant for diagnosis, as the method does not have to be absolutely quantitative, and differences may be allowed for. When determinations are made with the same patient from day to day, the same method of collecting the sample is used.

If the bag is washed out with 1000 c. c. of air following a determination, practically no acetone remains in the bag to interfere with subsequent determinations.

Within 30 seconds after collecting the specimen, it is blown through the Scott-Wilson acetone reagent.[4] About 25 c. c. of the reagent are placed in a large test-tube (30 mm. in diameter × 200 mm. in height); a blowing tube is used similar to that in Folin's micro method for ammonia. The liter of air is blown through the solution in about 30 seconds. At first we used two tubes in series each containing the reagent, but even when large amounts of acetone were present there was only a trace of cloudiness in the second tube. If acetone is present a white cloud is formed, which reaches its maximum density in about five minutes.

A standard solution of acetone is made up and standardized (Messinger titration), containing approximately .02 mg. per cubic centimeter. In making this solution, 5 c. c. of acetone are diluted to one liter (Solution I); 5 c. c. of this solution are in turn diluted to one liter (Solution II). Solution I is fairly stable and will keep for months, but Solution II should be made fresh every two days.

To 25 c. c. of Scott-Wilson reagent in a second tube one adds, according to the amount of acetone in the air test, 1 c. c., 5 c. c., 10 c. c. or 20 c. c. of Solution II; this is done as soon as possible after the air test has been made.

Comparison of the cloud in the tubes will tell the amount of acetone present. This is made more accurately by diluting the tubes with known and unknown amounts of acetone with water until approximately the same cloudiness is present in both; the amount of acetone in the breath is calculated from the volumes of fluid in the two tubes and the amount of acetone in the standard. A nephelometer[5] may be used if desired.

The amount of acetone present in one liter of air, even in cases in which there is a large amount, will give only a cloudy suspension, which makes comparison easy.

When this test is used, a normal person will show no acetone and the solution will remain clear.

.02 to .05 mg. acetone per 1000 c. c. air may be regarded as a trace.

.10 mg. per 1000 c. c. air is a moderate amount.

.20 mg. per 1000 c. c. air is a large amount.

.40 mg. per 1000 c. c. air is a very large amount.

Two determinations (duplicates) at the same time have always given practically the same results.

The following cases are of interest in showing the application of the method:

**Case A. M., boy, aged 9, admitted to the hospital on October 6 with diabetes, showing some hyperpnea and tendency to coma. The diet was limited to vegetables until October 8, when fasting was started. On October 10 he was sugar free and feeding was commenced. On October 13 he was receiving 13 gm. carbohydrate and 300 cals. On October 21 he was receiving 40 gm. carbohydrate and 1060 cals. Tolerance 100 gm. carbohydrate. The figures for acetone per liter expired air were as follows:**

| | | |
|---|---|---|
| Oct. 6..... .21 mg. | Oct. 9..... .18 mg. | Oct. 16..... .05 mg. |
| Oct. 7..... .20 mg. | Oct. 10..... .20 mg. | Oct. 18..... .03 mg. |
| Oct. 8..... .18 mg. | Oct. 13..... .05 mg. | Oct. 21..... .03 mg. |

**On October 6 the alkali reserve by the Van Slyke method was 25 vols. $CO_2$ per cent.**

**Case M. F. C., aged 12, and Case M. C., aged 16, were epileptic patients, who were treated by starvation to observe the effect on the convulsions. Acetone determinations in the breath were made in each case during the fast.**

| M. F. C. Day of fast | |
|---|---|
| 1. | .03 mg. |
| 2. | .30 |
| 3. | .44 |
| 4. | .50 |
| 5. | .70 |
| 6. | .70 |

| Day of feeding | |
|---|---|
| 1. | .33 |
| 2. | .15 |
| 3. | .00 |

**Alkali reserve = 41 vols. $CO_2$ per cent (Van Slyke) on last day of fast.**

| M. C. Day of fast | |
|---|---|
| 1. | .01 mg. |
| 2. | .04 |
| 3. | .11 |
| 4. | .10 |
| 5. | .09 |
| 6. | .05 |

**Alkali reserve = 38 vols. $CO_2$ per cent (Van Slyke) on last day of fast.**

The above is interesting in showing one patient who is very susceptible to acetone body acidosis, while the other is hardly susceptible at all.[6] This patient, M. F. C., shows the largest amount we have found. It is interesting to note that a high acetone in the breath does not necessarily mean a low alkali reserve (acidosis).

**Case C. B., aged 8½ months. Brought to the hospital at 9 a. m., having had approximately 20 green watery stools in the preceding 24 hours. He was drowsy, feverish, and with rapid deep respirations suggesting hyperpnea. Acetone in breath, .30 mg. per 1000 c. c. Only a trace was present 36 hours after the intravenous injection of 125 c. c. of 8 per cent glucose solution.**

[2] Jour. Physiol., 1911, xlii, 456.

[3] Jour. Biol. Chem., 1920, xliii, 57.

[4] Mercuric cyanide ..... 10 grams.
Sodium hydroxide ..... 180 grams.
Water .....1200 c. c.

The solution is shaken in a flask and 400 c. c. of a 0.7268 per cent of silver nitrate are added. This reagent will keep indefinitely, the clear fluid being decanted from the precipitate which tends to form.

[5] Marriott, Jour. Biol. Chem., 1913, xvi, 293.

[6] *Cf.* Higgins, Peabody and Fitz, Jour. Med. Res., 1916, xxxiv, 267.

# CERTAIN CULTURAL CHARACTERISTICS OF THE GONOCOCCUS

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AND
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1. *Introduction.*—As a consequence of the studies made in this laboratory, on the effects of disinfectants on the gonococcus, using the method of cultivating the gonococcus which has been described by Swartz,[1] we have found it desirable to make some investigations on the cultural characteristics of this organism. The ease and certainty with which profuse growth can be obtained by this method have simplified greatly the experiments made for the above purpose.

2. *Historical.*—The desirability of the presence of uncoagulated proteid in media for the gonococcus has been recognized since the day of Bumm.[2] Growths have been obtained on such media, placental serum,[3] blood serum,[3] ascitic fluid,[4] hydrocele fluid,[5] whole blood,[6] etc., being employed. Until recently, the growths have been described as scanty, and rather apt to die out upon repeated transfer. The morphology of individual colonies has been described in great detail.[7]

Vannod,[8] using a slightly alkaline medium, called attention to the necessity of careful adjustment of the reaction of the media; while Finger and others[9] stated that the best growth was obtained on slightly acid media. Martin,[7] using more accurate methods of measuring the reaction, recommended media having a reaction of pH 7.6, which is close to that of the body fluids, and claimed that the addition of body fluids to the media is of use principally as providing a buffer which regulates the reaction.

Hall[10] described a medium made with a watery extract,* which was boiled, of beef testicles. The juice of these organs was supposed to be especially favorable to the gonococcus. Stickel and Meyer[11] recommended a medium rich in ammo-acids and vitamines, after the principles of Cole and Lloyd.[12] The growths obtained with these media, however, were not much superior to those of the older investigators.

Wherry and Oliver[13] first called attention to the fact that the gonococcus is a microaerophile organism, and grows best at a reduced oxygen tension. They obtained profuse growths. Chapin[14] replaced part of the air in his culture tubes with $CO_2$, and felt that the presence of this gas was the important factor in securing good growth. Cohen and Fleming,[15] and Kohman,[16] working with the meningococcus, found that it, too, grows better at reduced oxygen tension. Kohman[16] concluded from his experiments that the superior growth of the meningococcus in closed systems was due entirely to the excess of moisture present and not to a decreased oxygen tension. He found that when grown in connection with a culture of *B. subtilis*, by the method of Wherry and Oliver,[13] the oxygen tension was reduced 9.5 to 15.3 per cent. Gates[17] concluded that, when the reduction is accomplished by substitution with $CO_2$, the beneficial results are due to the action of $CO_2$ in changing the reaction of the media. He found that the meningococci grew equally well in atmospheres containing from 15 to 40 per cent of oxygen, that the reaction must be pH 7.4, and that the presence of sufficient moisture is necessary for luxuriant growth. Reudiger[18] obtained good growth by simply stoppering his tubes tightly after inoculation. It is generally agreed that the gonococcus will not grow profusely under anaërobic conditions,[19] and that the best growth is obtained under aërobic conditions (2-b).

Brons (1907),[20] investigated the sugar reactions of the gonococcus, and found that dextrose was fermented with the production of acid but not gas, while maltose, levulose, saccharose, lactose and galactose were not fermented. This has been confirmed by others.[21]

It has been stated that gonococci, after long subculturing, may become Gram-positive. Vannod[8] and Martin[7] found that the organism would become, after a time, habituated to plain media containing no uncoagulated protein, and give good growth upon it.

Although investigators have been generally in agreement upon certain points, there is diversity of opinion on others. Thus, the sugar reactions of the gonococcus and the morphology of its colonies, as found by different workers, are the same. On the other hand, a number of quite different reactions have been recommended as the most suitable for the growth of the gonococcus, and while all have found the organisms to grow better in closed systems, it is doubtful whether this difference is due to lowered oxygen tension, increased $CO_2$ tension, change in reaction due to $CO_2$, or abundance of moisture. That the gonococcus should be able to accustom itself to plain media and become Gram-positive, are very important points, if true.

We have followed generally these lines in our work, also attempting to determine for the gonococcus, when grown in sugar media, an acid death-point like that described for *B. coli* by Michaelis and Marcora[22] and by Bruenn.[23]

3. *Growth on Culture Media.*—One strain of gonococcus in our series showed a very slight growth consisting of a few isolated colonies after being transplanted several times on the usual medium, and then transplanted to plain agar containing no uncoagulated protein. A second transfer produced no growth. Aside from this instance, our organisms have not grown on plain media, either when freshly isolated or after many subcultures in the laboratory.

Media made with ascitic fluid, hydrocele fluid, pleural fluid, rabbit serum, and cat cerebro-spinal fluid all showed good

growth. We may therefore conclude that the nature of the uncoagulated proteid present in the media is of minor importance. The same may be said of the quantity present, since some of our samples of fluid contained two or three times as much albumin as others.

On solid media isolated colonies of the gonococcus, which occurred under unfavorable conditions of growth, such as a too high oxygen tension or the presence of small quantities of some germicidal substance, presented the same appearances as those described by Martin[7] and others. A translucent gray color by reflected light, changing to a fairly clear light brown by transmitted light was found by us to be characteristic. Under favorable conditions, the growth formed a fairly thick film over the entire surface of the medium, in which individual colonies could not be distinguished. The same color and translucency were retained. The growth shows a definite tendency to cohere, and is rather mucoid in nature. It comes off easily from the medium in the form of flakes. We have never seen growth in the depths after stabbing the medium.

On liquid media consisting of two-thirds beef or veal infusion bouillon and one-third ascitic or hydrocele fluid, the gonococcus grows well when the oxygen tension is lowered. The medium is not clouded, the organisms growing in a pellicle on the surface. After a time, many organisms sink to the bottom, where they remain as a granular precipitate. As a consequence of this, one often sees delicate shreds and strings of organisms hanging from the lower surface of the pellicle.

After many subcultures, some of our strains grew with less profusion on solid media and showed many involution forms. We found that, if such a strain were passed once or twice through liquid media, the original profusion of growth was restored, and the involution forms diminished.

In liquid media containing the various sugars, we found the same fermentation characteristics described by Martin,[7] Brons,[20] Rothe,[21] Elser and Huntoon,[22] the gonococcus fermenting dextrose, with the production of acid, but not of maltose.

We have had little success with media containing no uncoagulated protein, such as those described by Cole and Lloyd,[23] Stickel and Meyer,[24] Hall,[19] and Clark.[18]

Microscopically, we have found the organisms always to be typical biscuit-shaped diplococci. In old cultures, involution forms, consisting of individual pairs larger than the average, are seen. These sometimes attain a diameter four or five times as great as that of normal cocci. Some strains seem more prone to the formation of involution forms than others. This does not, however, interfere with their vigor of growth.

None of our growths has ever shown the slightest tendency to irregularity of staining by the Gram method. Even after 20 or 30 subcultures, we have never seen any Gram-positive forms.

4. *Oxygen Tension.*—We have confirmed the results of previous workers as to the necessity of a reduced oxygen tension. It is immaterial whether this is obtained by exhausting part of the air, or by replacing it with $CO_2$. Using the method of Swartz,[1] * in which the pressure in the tube is reduced 7 to 10 per cent by first heating and then stoppering so as to make the tube air-tight, we have obtained very profuse growths on ascitic-fluid veal infusion agar. In desiccators from which part of the air is exhausted, we have observed good growth up to a 40 per cent exhaustion. The exact limits of pressure which will permit growth have not been determined. The growths at a 10 per cent reduction are luxuriant and not surpassed by those at any other pressure used by us. If, for any reason, the system is not closed, and atmospheric pressure obtains in the culture tube, the growths are always very strikingly reduced and sometimes do not appear at all. This is well shown in Fig. 1, *A* and *B*. The two tubes are from the same batch of media and were inoculated from the same vigorously growing culture. That in which the oxygen tension was reduced showed luxuriant growth, the other only a few colonies.

5. *Reaction.*—The usual media used by us had a reaction of pH 7.4. In order to determine the effect on growth of the initial reaction of the medium, a series of tubes was prepared, in which the usual medium (ascitic fluid veal infusion agar) was titrated, N/10 Na OH and N/10 HCL, and suitable indicators being employed, to a number of different reactions, both acid and alkaline. The indicators used, having no germicidal action, were allowed to remain in the medium, which after

* Briefly, the method is as follows: The medium employed is a 2 per cent beef or veal infusion agar, prepared in quite the ordinary manner, which is brought to a reaction of pH 7.6, phenolsulphonephthalein being used as an indicator. After autoclaving, the reaction having come to about pH 7.4, sterile ascitic, pleuritic or hydrocele fluid is added to the melted agar in the proportion of one part of fluid to two parts of agar. The tubes are then sealed with sterile rubber stoppers and slanted. This corking prevents evaporation, permits the medium to be kept in the incubator, facilitates the detection of any contamination and keeps the medium warm for inoculation at any time. The use of the rubber stopper has a further advantage in that it prevents contamination much more surely than the ordinary cotton stopper.

Inoculation is made as plentifully as possible. It is important to have the medium at body temperature when the inoculation is made, to keep it so thereafter, and to prevent cooling of the material before inoculation. Immediately after inoculation, the tube, held horizontally, is turned so that the agar slant is uppermost. Held by the butt, it is then passed longitudinally through the Bunsen flame about three or four times and quickly corked. Experiments with suitable apparatus show that this procedure keeps the air in the test-tube sufficiently to cause the pressure within to be lowered from 70 to 100 mm. of mercury (about 10 per cent of atmospheric pressure), when the tube is again cooled to 37.5° C. By this procedure the medium is not coagulated nor the gonococci harmed. By following this simple technique, we obtain with perfect regularity viable colonies in from 15 to 18 hours with profuse growth in 24 hours. The viability of the gonococcus on this medium is about 7 days. If other organisms are found to be present, plates may be made from the same medium and placed in the incubator in vacuum desiccators, in which the pressure has been lowered 10 per cent. Good growth may be obtained on fluid media prepared as above, except for the agar, and with or without sugar. The agar tubes should have, after hardening, a small quantity, about 0.5 c. c. of water of condensation in the lower angle of the slant. This assures the best growth.

titration was slanted and cooled. This insured that no change of reaction took place on cooling or later. The tubes were then inoculated from the same vigorously growing culture and cultivated at reduced oxygen tension in the usual manner. The results of such a series are shown in Table 1.

TABLE 1.—INITIAL pH OF MEDIA

| Gonococcus | 5.4 | 5.6 | 6.0 | 6.6 | 7.0 | 7.6 | 8.0 | 8.6 | 9.0 |
|---|---|---|---|---|---|---|---|---|---|
| 24-hour reading..... | 0 | 0 | 0 | + | + | + | + | 0 | 0 |
| 48-hour reading..... | 0 | 0 | 0 | + | + | + | + | 0 | 0 |
| 7-day reading..... | 0 | 0 | 0 | + | + | + | + | 0 | 0 |

The tubes at pH 6.6 and pH 8.0 showed growths perhaps slightly less luxuriant than the rest, but among the others no distinction could be made. Other conditions being favorable, then, there is a fairly wide range within which the initial reaction of the culture medium does not affect the growth of the gonococcus.

Other experiments were made, in which emulsions of gonococci were exposed to solutions of varying reactions for periods of 20 minutes, and then cultured on the usual media.[3] They are able to resist for this length of time the action of solutions from pH 4.5 to pH 8.5 inclusive, but an acid solution of pH 4.0 or an alkaline solution of pH 9.6 will kill them in 20 minutes.

6. *Moisture.*—We found that the presence of moisture in the culture media is desirable and indeed necessary for profuse growth. Tubes of culture media, stoppered with cotton and placed in the incubator, were allowed to dry until the medium cracked and no "water of condensation" remained. These tubes were then inoculated from a vigorously growing culture, stoppered, and cultivated at reduced oxygen tension in the usual manner. No growth occurred. Suitable controls showed the gonococci used to be viable. Several days later, the corks were removed from these tubes, sterile ascitic fluid was added until there was about 1 c. c. excess in the lower angle of the slant, and they were reinoculated and cultivated as before. Luxuriant growth took place. This experiment merely confirmed our observations over a long period of gonococcus cultivation, during which dried-out media always gave inferior growth.

That moisture alone, in the absence of reduced oxygen tension, will not give luxuriant growth, was proved in the following manner: Several tubes were inoculated from a vigorously growing culture. Half of them were stoppered with cotton, and placed in a large desiccator, the bottom of which was covered with a layer of water containing some half-immersed gauze to provide a large surface of evaporation. The entire desiccator was placed in the incubator without altering the atmospheric pressure within. This arrangement prevented any drying of the media, and maintained the water-vapor tension of the air at a high point. The remaining tubes were stoppered and cultivated at reduced oxygen tension in the usual manner. In all the stoppered tubes profuse growth occurred in 24 hours, while in those in the desiccator only a very few colonies appeared in 48 hours, the contrast being very striking. After 48 hours, one of the tubes from the desiccator was heated, stoppered and cultivated in the usual manner. Numerous colonies appeared in 24 hours, showing that although the gonococci were present and alive, their growth, even in the presence of abundant moisture, had been inhibited by a too high oxygen tension.

FIG. 1.—*A*, 24-hour growth gonococcus in reduced atmospheric tension. *B*, 24-hour growth, same strain gonococcus on same medium, at ordinary atmospheric tension.

The experiments described in paragraphs 4, 5 and 6 seem to us to prove conclusively that the most important factor in the profuse growth of gonococcus in closed systems is reduced oxygen tension. It cannot be the presence of $CO_2$, since in our work the reduction of pressure has been attained by simply removing part of the air. This too would eliminate any change in the reaction of the media, due to the presence of an excess of $CO_2$, and in addition the experiments described in paragraph 5 show beyond dispute that small changes in the reaction

of the medium are a matter of indifference in the initial growth of the gonococcus. The presence or absence of moisture will not determine a profuse growth if the oxygen tension is not lowered. We may conclude, therefore, that the original deduction of Wherry and Oliver,[13] that the gonococcus is a microaerophile organism, and that a reduced oxygen tension is essential to its best growth, is correct.

7. *Changes in Reaction on Growth.*—In order to determine the acid death point for the gonococcus, cultures were made in liquid media containing 1, 2 or 3 per cent dextrose. Our experience showed that after ten days' incubation all growth had ceased, and that there were no more living organisms. Hence, after the tubes had been left for at least ten days in the incubator, the acidity of the media was tested colorimetrically and electrometrically.

The " acid death-point " by this method for gonococci grown in dextrose ascitic fluid bouillon is pH 5.6, the variations mentioned in the quantity of dextrose present making no difference.

The gonococcus always produces acid when grown on our ordinary ascitic or hydrocele fluid beef or veal infusion agar, the final pH being 6.2. This medium is not especially rendered sugar-free, but contains no reducing substance for Fehling's solution.

## CONCLUSIONS

1. The superior growth of gonococcus in closed systems, when part of the air or of the oxygen has been removed or replaced, is essentially due to the lowered oxygen tension, and not to moisture, change of reaction, or presence of $CO_2$.

2. Moisture is however necessary to good growth.

3. A reduction in the oxygen tension of 10 per cent is sufficient to produce optimal growth.

4. The gonococcus will grow luxuriantly, if the oxygen tension is suitable and moisture and uncoagulated proteid are present, on media having an initial reaction anywhere between pH 6.6 and pH 8.0 inclusive.

5. In dextrose-containing media, the acid end-point for the gonococcus is pH 5.6.

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# A LABORATORY METHOD FOR THE PREPARATION OF FIBRINOGEN[1]

By JAY MCLEAN

*(From the Physiological Laboratory of The Johns Hopkins University)*

An exasperating difficulty is frequently encountered in preparing fibrinogen by the method which employs sodium chloride to salt it out of solution. This difficulty is the insolubility of the final precipitate of fibrinogen in dilute sodium chloride solution, a condition that renders it useless for experimental purposes.

In this method the first precipitate of fibrinogen usually dissolves without difficulty in a 1 per cent solution of sodium chloride. The second precipitate, frequently a tough membrane-like flake, sometimes fails to dissolve, even after stirring with a glass rod for 30 minutes or longer. When the second precipitation does dissolve, it is difficult to purify it by another precipitation, as the third precipitate is very frequently insoluble.

By substituting, at Dr. Howell's suggestion, ammonium sulphate for sodium chloride to salt out the fibrinogen a readily soluble precipitated fibrinogen was secured. No difficulty has been encountered in dissolving fibrinogen which has been re-precipitated three times. Thus a fibrinogen freer from prothrombin, which tends to adhere to the precipitate, may be obtained.

A concentration of ammonium sulphate in the plasma adequate to cause complete precipitation of the fibrinogen for physiological purposes and not of the other plasma proteins was found to be one part of saturated ammonium sulphate solution to four parts of oxalated plasma. Concentrations above this bring down some of the paraglobulin. To determine this fact fibrinogen was precipitated from five equal volumes of plasma drawn at the same time from one dog. In four of the tubes saturated ammonium sulphate solution was added, giving final concentrations of the salt in the plasma of 16, 20, 23 and 26 per cent. In the fifth tube of plasma precipitation was caused by sodium chloride, one part of the saturated solution to one part of plasma. The concentration of one part saturated ammonium sulphate to four parts of plasma brings down practically all of the fibrinogen. The solutions of fibrinogen secured from the above precipitates were filtered and the filtrates heated slowly in a water bath to just 60 degrees in order to coagulate the fibrinogen. The contents of all the tubes were then filtered and the filtrates were heated up to 85 degrees. The solutions of proteins precipitated by a concentration of ammonium sulphate greater than 20 per cent became distinctly opalescent, demonstrating the presence of paraglobulin. The solutions of protein precipitated by ammonium sulphate in concentration of 20 per cent or 16 per cent, and by sodium chloride in concentration of 50 per cent, remained clear or developed sometimes but the slightest opalescence. As the concentration of one part of saturated ammonium sulphate to four parts of oxalated plasma brought down as much fibrinogen as the sodium chloride method and did not practically contain any paraglobulin this concentration was selected as being adequate.

The details of the preparation of fibrinogen by the use of ammonium sulphate as a precipitant are:

1. Use cat's or dog's blood, oxalated and centrifugalized for 20 minutes. Carefully pour or pipette off the clear plasma.

2. Add to the plasma one-fourth of its volume of saturated solution of ammonium sulphate. Centrifugalize the precipitate promptly for five minutes. Pour off the supernatant fluid. Carefully wash the precipitate at least twice by layering over it one-fifth saturated solution of ammonium sulphate. Add to the washed precipitate a volume of 2 per cent sodium chloride equal to that of the original plasma and stir gently with a glass rod until dissolved. Filter the solution.

3. Precipitate the solution by adding one-fourth of its volume of saturated ammonium sulphate solution. Centrifugalize promptly for five minutes. Pour off the supernatant liquid and drain. Wash for some minutes in one-fifth saturated solution of ammonium sulphate and drain. Wipe the inside of the glass centrifuge tube with filter paper. Dissolve in 1 per cent sodium chloride solution and filter. This process may be repeated a third time but usually two precipitations suffice.

The solution should clot in a few minutes on the addition of thrombin or prothrombin and calcium, and should not clot in 24 hours either spontaneously or on the addition of calcium chloride.

Fibrinogen prepared by using sodium chloride has time and again failed to go into solution, whereas fibrinogen prepared from the same plasma, but precipitated with ammonium sulphate, dissolved rapidly.

[1] Work done under the tenure of the Le Conte Memorial Fellowship of the University of California, 1918-1919.

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# RESTORATION OF HEARING IN A CASE OF GUNSHOT INJURY OF THE EUSTACHIAN TUBES

By John W. Baylor

*(From the Department of Surgery, The Johns Hopkins University and Hospital)*

Many of the technical difficulties of an examination of the ear, nose and throat have been removed by the introduction of electrically lighted instruments. The nasopharyngoscope, devised by Dr. Edgar M. Holmes of Boston, is especially valuable for the diagnosis of infections of the posterior ethmoidal and sphenoidal sinuses, and for the inspection and treatment of the Eustachian tubes. It is true that the use of the nasopharyngoscope is not essential for the diagnosis and treatment of the majority of cases, and it is only by constant practice that one acquires sufficient skill to use it to advantage in the cases that could not be treated by the ordinary methods. For the past five years we have used this instrument in the examination of all nose and throat cases and in the treatment of all Eustachian tube conditions, and it is to this fact that we ascribe the successful outcome in the following case:

F. N., white, aged 28. Surgical Nos. 50309 and 50448, Medical No. 43470.

The patient was admitted to The Johns Hopkins Hospital February 20, 1920, complaining of deafness in both ears that had resulted from gunshot wound received two years before. The bullet from a 38 caliber pistol had entered the right side of his face 1 cm. in front of the tragus at the lower border of the zygoma, and passed downward at an angle of about 35 degrees. He developed a temporary facial palsy and a subjective hemianesthesia, both on the right side. Immediately after the accident he was confined to bed for three weeks in a nospital in Tennessee. No attempt was made to remove the bullet. His hearing was subjectively normal during this period. A short time later he noticed some impairment of hearing in the right ear, and in six or seven months this had progressed to almost complete deafness. There was a discharge from the left ear for two or three months. This did not appear until four weeks after the injury and was not associated with earache. Hearing gradually became impaired on this side also, but to a lesser degree than on the right.

On admission, there is no discharge from either ear. The drums are retracted and thickened.

Hearing Tests

| RIGHT EAR | LEFT EAR |
|---|---|
| Loud shouts heard but not understood (a Bárány Lärmapparat employed). | Whispers not heard. Conversational tone understood at a distance of 12 inches. |

Bone conduction is lengthened on both sides.

Vestibular tests are normal.

The naso-pharynx is filled with scar tissue. The pharyngeal orifices of the Eustachian tubes and the fossæ of Rosenmüller are not recognizable.

From the history of the onset of deafness, the appearance of the naso-pharynx, and from the X-ray localization, it is apparent that the bullet passed through the naso-pharynx and injured both Eustachian tubes.

The plan of treatment was to excise the scar tissue in the naso-pharynx and, after the wound had healed, to locate the orifices of the Eustachian tubes with the aid of an electric nasopharyngoscope and to try and restore their patency by dilatation and inflation.

On February 24, 1920, the patient was anesthetized and placed in the Trendelenburg position. The soft palate was retracted by means of small rubber catheters passed through each nostril and brought out through the mouth.[1]

The tissues of the naso-pharynx were infiltrated with procaine and adrenalin in order to control bleeding partially, and to diminish the reflexes that invariably occur during operative procedures in the naso-pharynx.[2]

Even under direct vision the orifices of the Eustachian tubes could not be recognized. The scar tissue was removed by sharp dissection and with sharp nasal rongeurs. The bleeding was controlled wherever possible by the introduction of catgut sutures. The naso-pharynx was not packed.

The post-operative course was uneventful until the fifth day when a bronchopneumonia developed on the right side. The patient was transferred to the medical service where he remained until March 28, 1920, at which time he had completely recovered. Nothing was done to the naso-pharynx during this period with the exception of frequent irrigations with sterile normal salt solution, followed by the introduction of sterile albolene into each nostril.

During the next three months about three hours a week were devoted to the localization and dilatation of the Eustachian tubes.[3]

[1] Ether anesthesia was given through the mouth-gag used for tonsillectomies. A good illustration of it is to be found in an article by Crowe, Watkins and Rothholz in The Johns Hopkins Hospital Bulletin, 1918, XXVIII, p. 18, Fig. 9.

[2] When adenoids are removed even under light ether anesthesia there is almost invariably an interruption of the respiratory rhythm. We have had one death due to spasmodic closure of the glottis and to arrested heart action, presumably caused by stimulation of the vagus. This occurred during the removal of a large metallic foreign body that had been present in the naso-pharynx of a child for several months.

[3] For several years we have used the electric nasopharyngoscope for the introduction of the catheter and the dilatation of strictures of the Eustachian tube. If sufficient time is devoted to the anesthetization of the nose, naso-pharynx and the Eustachian tubes, the entire procedure may be carried out with but very little discomfort to the patient.

The floor of the nose, the lower border of the inferior turbinate and the naso-pharynx on each side are cocainized. For this purpose we prefer to use a small piece of cotton on an applicator, with a 20 per cent solution of cocaine, rather than to use a weaker solution in a spray. If the excess of cocaine is removed by pressing the cotton between two layers of gauze there is no danger of poisoning in this method of anesthetization.

The nasopharyngoscope is then introduced along the floor of the nose on one side, and the Eustachian applicator, moistened with a 20 per cent solution of cocaine, is passed through the other nostril and into the orifice of the Eustachian tube. If left in place for five minutes, the Eustachian tube will be sufficiently anesthetized to permit the catheterization and subsequent passage of bougies without pain.

The catheters and the soft rubber ear syringe used for inflation are sterilized by boiling. The whalebone bougies are placed in a 1-1000 solution of bichloride of mercury and are allowed to remain for 15 minutes. The tip of the bougie is dipped into sterile olive oil or vaseline in order to render its passage along the Eustachian tube less irritating.

Even with the magnification and the brilliant illumination of the naso-pharynx that is obtained by the use of the naso-pharyngoscope, it was extremely difficult to find the orifices of the Eustachian tubes.

On the left side there was no Eustachian cushion and for many days we were unable to localize the orifice of the tube. On one occasion, however, a small plug of mucus was seen to be forced out of a minute opening during the act of swallowing. The smallest sized catheter was then placed directly over this area and by inflation and the use of the diagnostic tube it was demonstrated that this small opening led into the Eustachian tube. Immediately following this first inflation there was marked improvement in hearing on the left side. It is noteworthy that the improvement was permanent and the deafness did not return in two or three days, as is usual in chronic inflammatory conditions of the Eustachian tube.

On the right side the Eustachian cushion was present, but attempts to inflate and to pass bougies indicated that the tube had been divided a few millimeters above the pharyngeal orifice. The pinpoint opening of the tube was located only after many hours of observation, probing, and attempts to inflate. Once the opening was located, however, inflations and dilatations with whalebone bougies rapidly restored the hearing. From attempts to pass bougies it was apparent that there was a further stricture higher up the tube. This was probably due to the fact that the bullet had entered the right side and caused more extensive damage to the right tube than to the one on the left.

After three months of treatment the patient is able to hear from the balcony of a theatre for the first time since the accident. Ordinary conversation can be heard from any part of the room. A low tone tuning-fork, $C_{128}$, can be heard by air conduction on both sides. Air conduction and bone conduction are about equal in the left ear (June 21, 1920). The hearing in the right ear still remains slightly impaired and bone conduction is a little better than air conduction.

With this improvement in hearing there has been no appreciable change in the appearance of the tympanic membrane on either side.

It is possible that the scar-tissue will ultimately contract and again produce stenosis, but subsequent treatments should not be more difficult than in ordinary strictures of the Eustachian tube. The point we wish to emphasize is that it would have been impossible to have benefited this patient in any way without the use of the electrically lighted nasopharyngoscope.

# THE HISTOLOGICAL PATHOLOGY OF A CASE OF MEASLES CONJUNCTIVITIS

By JOHN R. PAUL

*(From the Department of Pathology, The Johns Hopkins University)*

Despite the great importance of measles and our increasing familiarity with the serious proportions which the complications of this disease may assume, our knowledge of its pathological anatomy is quite limited. The most specific and in fact practically the only typical lesions which have been investigated are those which appear on the skin and buccal mucosa. Various workers have described these lesions, among whom may be mentioned Von Jürgenson [1] and Ewing.[2] Quite recently Mallory [3] has made a histological investigation of the development of the skin eruption in measles and of the Koplik spots, by studying serial sections of these lesions excised from patients at various stages of the disease.

A great deal of attention has been brought to bear on the more serious complications of measles, especially the pneumonia. Detailed accounts of the pathological anatomy can be found in the studies of Steinhaus,[4] Hecht,[5] MacCallum [6] and others.

Thus far, however, the conjunctivitis of measles has not been of more than passing interest. Classified by ophthalmologists under the general heading of exanthematous conjunctivitis, it is regarded as being practically similar in all respects to the simple forms of acute catarrhal conjunctivitis with no particular specific features (Fuchs).[7] Despite its mild and nonspecific character, however, it is generally considered to be due primarily to the actual causative agent of measles, and in that respect it is important. From a pathological standpoint it has received very little attention, in all probability because of the mild and transient nature of the conjunctivitis, and partly also of the difficulty in obtaining satisfactory material for study. The literature seems to contain very few descriptions of the histological pathology of specimens of measles conjunctivitis. Stargardt [8] speaks of one specimen in connection with a list of allied conjunctivitides, without giving any adequate description; six specimens are reported by Frosche,[9] who similarly makes no mention of their specific characteristics.

The material investigated in this instance was obtained from a case of measles which was under observation in the Harriet Lane Home for Invalid Children from March 29-31, 1920.

The patient, a male colored baby only two months old, had probably been premature, weighing only four pounds at birth. He had been breast fed until two weeks before admission to the hospital. Breast feedings had been stopped when, at this time, the mother suddenly became ill, developing a sore throat, fever and a marked rash. A diagnosis of measles was made and the child was immediately isolated from the mother. He did not do well on artificial feedings and 11 days after isolation from the mother also developed fever and a reddish maculo-papular skin eruption; this was accompanied by profuse running from the eyes and nose. On the following day signs of pneumonia were noted in the chest. The temperature remained elevated and the leukocyte count was 8,400. The child died on the third day after the appearance of the rash.

The body was given to the State Anatomical Board for disposal and a complete autopsy was performed 18 hours after the child's death.

The body showed a fair degree of nourishment. Over the skin there was a well defined macular rash especially prominent over the face, chest and back. The eyes showed injection of both bulbar and palpebral conjunctivæ and there was marked œdema of the lids. No Koplik spots were observed on the buccal mucosa at the time of autopsy. A small amount of fluid was encountered in both pleural cavities from which a pure culture of *B. influenzæ* was obtained. The lungs showed bronchopneumonia with bilateral involvement of the lower lobes. The smaller bronchi were found to be plugged with a thick muco-purulent exudate surrounded by small isolated areas of consolidated peribronchial alveoli. Cultures of *Diplococcus pneumoniæ* and *B. influenzæ* were obtained from the lungs, and the former was also grown from a heart's blood culture taken at the time of autopsy. The other organs did not show any gross changes apart from incidental findings, with no direct bearing on the case. These included a slight congenital stricture of the left ureter and an organizing and ossifying subperiosteal hematoma of one of the parietal bones of the skull.

The material for histological study was fixed in Zenker-formol solution; paraffin sections were cut and stained with hæmatoxylin and eosin.

The lung sections showed a typical early, but not extensive, interstitial bronchopneumonia. Sections of the liver and thymus gland showed areas of focal necrosis. Sections through some of the skin lesions revealed changes which for the most part were of a minor character. Principally they amounted to localized areas of vacuolization of the epidermal epithelium and a scanty infiltration of wandering and small round cells into the corium which largely tended to be perivascular in distribution.

For the study of the conjunctiva, sections of both upper eyelids were used, stained with hæmatoxylin and eosin, Van Gieson's, Leishmann's and bacterial stains.

In summarizing the changes found in the eyelid a review of the normal appearance of this structure may be useful. The normal histological picture of the eyelid is divided by anatomists into five layers, which from without inwards include: (1) Skin, (2) subcutaneous tissue, (3) muscular layer (M. orbicularis oculi), (4) tarso-fascial layer, which includes the tarsal plate, composed of dense fibrous tissue, and lodges the Meibomian glands, (5) conjunctiva.

Here we shall deal more especially with the conjunctiva and the tissue lying directly beneath it. The former is generally divided into two parts, the tarsal conjunctiva and the conjunctiva fornicis. Over the tarsus it is tightly adherent to the underlying fibrous plate presenting a smooth flat surface. Above the upper border of the fibrous plate, it becomes the conjunctiva fornicis. Here the surface is elevated into large folds, and beneath it there is loose fibro-elastic tissue. The conjunctival epithelium itself is pseudo-stratified in type. Beginning at the free edge of the eyelid we have a transition of the epidermis into conjunctival epithelium, the latter consisting approximately of two layers, a top layer of cylindrical cells and a deeper layer of smaller rounder cells. This regularity is not, however, constant; for we have in the tarsal conjunctiva low but genuine papillæ, which consist of slight elevations with vessels and surrounding stroma, between which the epithelium dips. On the apex of the papillary prominences the epithelium retains its regular two-layered form, but in order to maintain a flat surface, between them, other cells appear in the depressions so that here several layers are produced. This continues up to the convex border of the tarsus, where not only are the papillæ higher but the surface of the epithelium dips down between them, forming sulci. With the increase in the size of these folds in the conjunctiva fornicis the invaginations often assume greater proportions, appearing in some instances like tubular glands commonly described as Henle's glands.

Below the epithelium, a well defined tunica propria is present, beneath which are many lymphatic spaces and small vessels. We also find many small nests of alveolar glands partly along the convex border of the tarsus and partly in the fornix—Krause's glands, probably performing the function of accessory tear glands. Owing to the exposed situation of the conjunctiva, signs of low-grade inflammation are a constant finding in the subepithelial tissues. After the first four to six weeks of life a thin layer of infiltrating lymphatic and wandering cells appears below the stratum proprium. This layer is thickest in the receding portion of the conjunctiva fornicis, where collections of lymphocytes appear often as cell nests but not true lymph follicles. These infiltrating cells extend just below the epithelium as a thin tapering line which ends before reaching the free edge of the lid.

The conjunctiva is exposed to external influences more than any other mucous membrane in the body (Fuchs).[1] This then is probably the cause of the variations in number and activity of the reacting cells that underly the epithelium—namely, the plasma cells and lymphocytes which are present in any healthy conjunctiva, but which are subject to variations. The size of the papillæ and the adenoid structure of the conjunctiva also probably stand in relationship to the amount of irritation which has been present, for in various types of mild conjunctival inflammations we see increasing surface irregularities, new formation of Henle's glands and even cyst-like formations (Mayou).[2] The fact remains, however, that in the normal eyelid there are great individual variations and a line between physiological and pathological states cannot be sharply drawn. In the present instance the sections which are under investigation do not show changes that differ in any marked degree from the normal picture, but most of the factors which we commonly recognize as signs of reaction to an abnormal amount of irritation are prominent or increased.

The changes seen in these sections can be briefly summarized as: The œdematous appearance of the lid in general, dilatation of the Meibomian glands, epithelial degeneration and subepithelial reaction. The œdema of the eyelid is characterized in the section by a general looseness of structure and a loss of the compact appearance seen in normal sections. The lids show a definite increase in width, produced especially by the widening of the loose areolar and muscular tissue between the

tarsal plates and the skin. Here and there the presence of fluid, in the form of granular debris, can be detected among the loose connective-tissue fibrillæ.

The widely dilated lumina of the Meibomian glands are prominent. Most of the different acini contain mucous secretion appearing in the section as a rather granular reticulum.

More definite, however, is the presence of epithelial degeneration. Some of it is unquestionably part of a post-mortem process, but this is not sufficient to mask materially the other changes. In general, the conjunctival surface is more irregular; the papillæ are very prominent and the increase of interpapillary invaginations causes the epithelium to appear as if it were almost universally stratified and consisted of more than the usual two cells in thickness. The smooth outer edge of the conjunctival epithelium is replaced by a very irregular one. Along it, quantities of desquamating cells are seen, some wholly and others partly detached, while as a rule nearly all of the outer cells are losing their compact arrangement and are tending to separate from one another, leaving intercellular spaces. In some instances, especially near the free edge of the lid, groups of superficial cells are partially dissected away from the lower layer, leaving large clear spaces beneath them which contain either coagulated fluid or often groups of necrotic wandering and epithelial cells. The inner layer of epithelium shows beginning cellular degeneration here and there, with darkening of the nuclei and changes in the cytoplasm, which for the most part consist of the appearance of small clear vacuoles about the cell nuclei. In and about these areas of epithelial degeneration there are a few wandering cells, most of which show small dark pyknotic nuclei.

It is interesting to note that the stratified epithelium of the adjacent Meibomian glands shows changes somewhat similar to those seen in the conjunctiva. The glandular epithelium is in an infinitely better state of preservation, but again there are localized areas in which the cells show vacuolization of their cytoplasm with eccentric, shrunken, or contracted nuclei. In other areas there is mucoid degeneration of the epithelial cells. Wandering cells are apparently not attracted by these areas of degeneration of the glandular epithelium and there is a noticeable absence of any submucous cellular reaction comparable with that seen beneath the conjunctiva.

The accessory tear glands of the conjunctiva fornicis, whose epithelium more nearly approaches the conjunctival type, also show changes. Colloid-like material and leucocytes are seen in many of the lumina of the branching tubular glands. Changes of the actual epithelium are scarce, but there is some vacuolization of the cells and many contain large round granules or droplets of varying size. These seem to be frequent in the more remote portions of the gland. There is a distinct reaction of infiltrating cells in the subepithelial layers in contrast to its absence in association with the Meibomian glands. In this connection, however, it is well to emphasize the fact that here the tissue is of an extremely loose nature, whereas the Meibomian glands offer practically no loose peri-epithelial spaces and are tightly enclosed in dense fibrous tissue.

In the subconjunctival tissues the presence of a reaction of wandering cells is definitely seen. As mentioned above, normally there is a compact layer of lymphoid and wandering cells distributed beneath the surface epithelium. The appearance of these underlying cells is, however, unlike the normal picture. Between the tarsal conjunctiva and its underlying fibrous plate the infiltrating cells do not seem to be particularly increased in number, but instead of a thin even layer of cells, sharply limited to the tissue directly underlying the epithelium, the reacting cells here seem to be more diffusely scattered, penetrating slightly into the outlying layers of the tarsal plate and extending occasionally through the membrana propria, masking somewhat the line of demarcation between epithelial and subepithelial tissues. Most of the infiltrating cells are large wandering cells with distinctly irregular but not lobulated nuclei. There is a conspicuous absence of polymorphonuclear leukocytes in the reaction, but with the wandering cells there are a few small round cells and an occasional eosinophile.

As regards the distribution of these infiltrating leukocytes, in the tarsal conjunctiva it cannot be said that they follow any definite rule. No perivascular grouping is demonstrable here, the cells occupy the limited area of loose submucous space and the prominent papillæ diffusely. The picture in the other portion of the conjuctiva is similar, but the presence of infiltrating wandering cells is encountered much deeper in the looser underlying tissue. The large wandering cells here seem to be more definitely in association with the small vessels. Small irregular groups consisting of a dozen or more cells are occasionally seen around one of the underlying capillaries. As a rule, these cells are younger than those described beneath the tarsal conjunctiva and more perfect, appearing as beautiful large oval cells with round nuclei, eccentrically placed.

Signs of cell proliferation are not conspicuous. A careful search for mitotic figures among not only the reacting cells but also the epithelial cells revealed only a very few in each section. Most of these were found among the leukocytes beneath the glands of the conjunctiva fornicis.

One noticeable feature about the reacting cells, however, is the large number of isolated necrotic cells. These are seen in all stages, from cells showing darkened nuclei to others in which the nucleus has become densely pyknotic, contracted and shrunken. Many show various stages of nuclear fragmentation and karyorrhexis, so that small pyknotic masses of nuclear material, for the most part round but differing in size from that of a small coccus to a red cell, are seen scattered in close association with living infiltrating cells, especially near the free edge of the lid. Groups of these cell fragments are seen within the bodies of large phagocytic cells, often filling them completely and presenting a mulberry-like appearance. This type of necrosis is perhaps the most characteristic feature presented by the section.

As a whole, therefore, the histological picture seems to be that of a diffuse type of injury to the surface, and to a lesser degree, to the glandular epithelium, calling forth a reaction in the subepithelial spaces of endothelial leucocytes which are prone to undergo necrosis easily.

The relation of bacteria to conjunctivitis of this type is not fully appreciated, but the consensus of opinion is that the

organisms which have thus far been described as occurring in the conjunctivitis of measles play the rôle of secondary invaders. Staphylococci are frequently cultured and also Streptococci (Schottelius)."

No cultures were taken from the conjunctiva of this case. Sections, however, were stained to show bacteria in the tissues by MacCallum's method.[12] These show large numbers of organisms along the surface epithelium. They are present for the most part upon the lower half or more exposed portion of the conjunctiva. Diplococci predominate but many appear in short chains and often in well defined clumps among the surface irregularities and superficial intercellular spaces. Occasionally they are seen within the cytoplasm of exposed dying or desquamating epithelial cells; they do not, however, seem to penetrate deeper into the tissue and a careful search through the subepithelial layers does not show any demonstrable bacteria. Those present on the surface probably play the rôle of secondary invaders and some of them unquestionably represent a post-mortem growth.

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# LYMPHOSARCOMA, LYMPHATIC LEUKÆMIA, LEUKOSARCOMA, HODGKIN'S DISEASE

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The purpose of this communication is to summarize a study of 123 cases of lymphosarcoma, lymphatic leukæmia, leukosarcoma and Hodgkin's disease. Complete histories, autopsy protocols, and charts, with a concise review of the literature, will be published in The Johns Hopkins Hospital Reports for 1921. It is sufficient here to comment upon the present status of the above conditions, outline results obtained in the survey of each group, and propose a more simple classification.

To-day, under the term "lymphatic leukæmia," it is customary to include all cases with a permanent increase in the lymphocytes of the blood associated with a hyperplasia of the lymphoid tissue. Cases of general glandular enlargement, infiltration of parenchymatous organs and bone marrow, but no clinical blood changes (pseudoleukæmia) as well as cases of leukæmia with an invasive tumor (leukosarcoma), are usually wedged into this group. "Lymphosarcoma" has so far lost the meaning assigned to it by Kundrat, that it seems to include everything from his strictly localized invasive tumor to such a case as has been recently described by Schnyder. The patient was a white male, aged 17 years, who three weeks before death, developed pains in his back, dyspnœa, and weakness. The blood count showed a leukocytosis of 12,300 with polymorphonuclears 69 per cent and lymphocytes 13 per cent. Autopsy showed an invasive tumor of the mediastinum and pleura with involvement of lymph glands, adrenals, kidneys, liver, gall-bladder, dura mater, femur, tonsils and tongue follicles. "Hodgkin's disease" is usually considered to be an entity. But the ever increasing "intermediate forms and transitional stages" between lymphatic leukæmia and lymphosarcoma and between lymphosarcoma and Hodgkin's disease, augment beyond reason the power of the personal equation.

## LYMPHOSARCOMA

Ten cases from the autopsy records of The Johns Hopkins Hospital may be grouped according to the location of the primary tumor. Those starting in the intestines, six in number, presented several points worthy of mention. (1) The disease tends to occur in young individuals. (2) The disease runs a rapid course, usually within one year. (3) Abdominal discomfort, loss of weight and malaise, are characteristic symptoms and abdominal tumor masses may be noted clinically. (4) At autopsy the findings are surprisingly similar. Single or multiple tumors of the small intestine (five cases) or of the mesenteric glands (one case) are encountered. These tumors spread locally to infiltrate retroperitoneal tissues, glands, adrenals, pancreas, etc. But further extension to the spleen, liver and kidneys, lymph glands, deep and superficial, testicles and bone marrow, which occurs so characteristically, must take place by way of the blood stream. Another point of predilection for this tumor formation seems to be in the glands

of the mediastinum but this series, also (four cases) is small for statistical study. Similarity to the abdominal group, however, as regards mode of extension, is striking. The tumor may be strictly localized or may spread progressively by way of the blood stream.

### LYMPHATIC LEUKÆMIA

In the study of 15 cases of lymphatic leukæmia, three showed at autopsy hyperplastic changes in the lymphoid tissue. Clinically, however, the blood could not definitely be termed leukæmic, although the morphology and relative number of the lymphocytes were altered. An excellent discussion of similar cases by Fraenkel and Sternberg may be found in the Proceedings of the German Pathological Society for 1912. The Society recognized the intimate relationship between such "pseudoleukæmic" cases and true lymphatic leukæmia, mentioned examples where the one had progressed into the other, spoke of other cases where at autopsy the two conditions were indistinguishable, and concluded that the term "pseudoleukæmia" was superfluous and should be abandoned. Two cases with leukæmic blood pictures showed at autopsy infiltration of the parenchymatous organs and bone marrow but a sharp limitation of lymphoid hyperplasia to the mesenteric and retroperitoneal glands. Nine cases with leukæmic blood, general hyperplasia of lymphoid tissue, and infiltration of parenchymatous organs and bone marrow, were quite typical. One case observed for over three years gradually developed large invasive tumor masses of the inguinal and retroperitoneal glands.

### LEUKOSARCOMA

Leukosarcoma was used by Sternberg to designate a group of cases characterized by a leukæmic blood picture and an invasive lymphoid tumor. The origin of this tumor, neoplastic in nature, might be anywhere—breasts, skull, mediastinum. The blood picture, according to him, is not that of a small lymphocytic leukæmia but shows a high percentage of large lymphoid or "leukosarcoma" cells. Helly apparently goes further by differentiating leukosarcoma (a true neoplastic tumor) according to its association with "lymphopenia, sublymphæmia, or lymphæmia." On the other hand, Türck and Naegeli believe that leukosarcoma is only a stage of lymphatic leukæmia.

Four cases taken from the autopsy records of The Johns Hopkins Hospital and 22 cases collected from the literature were summarized. From this study it was possible to derive a more precise knowledge of the clinical course and pathology of this group and more accurately to discuss its relationship with allied conditions: (1) In 24 cases (92 per cent) the disease occurred in young individuals between the age of 7 and 30 years. (2) Loss of weight, malaise, chest symptoms, and glandular swellings, are prominent symptoms. (3) Leukæmic blood, lymphoid in type, large liver and spleen, general glandular enlargement with a tumor mass in the mediastinum or elsewhere may be looked for clinically. (4) The disease runs an acute course; 25 (96 per cent) of the 26 patients died within one year after the onset. (5) At autopsy the findings are characteristic and may be summarized as follows: (a) General glandular enlargement (85+ per cent); (b) infiltration of parenchymatous organs (100 per cent) and bone marrow; (c) an invasive mediastinal tumor spreading more or less to pleura, diaphragm and pericardium, in 21 cases, (84+ per cent); (d) microscopically, uniform extensive infiltration of lymphoid cells, measuring 5-6 $\mu$ in diameter, with little cytoplasm and a nucleus containing coarse chromatin granules. Mitotic figures may or may not be present.

### HODGKIN'S DISEASE

Twelve cases of Hodgkin's disease, taken from the autopsy records of The Johns Hopkins Hospital, have been reviewed. Nine cases are typical examples of Hodgkin's disease as described by Reed and Ziegler. They all presented general glandular enlargement with involvement of liver and spleen. Tuberculosis was present in two cases; three cases showed invasive tumor masses associated with the mediastinal or cervical glands. Microscopically, (1) alteration of the normal architecture, (2) appearance of lymphoid cells, (3) decrease in normal lymphocytes, (4) increase in connective-tissue stroma, (5) and diffuse endothelioid hyperplasia with large irregular mononclear and polynuclear giant cells, were constant. Eosinophiles were present in three cases. Three acute cases subjected to radium, difficult to classify, showed at autopsy a general glandular enlargement with involvement of liver and spleen. Lymphoid cells predominated. The total number of cells was not decreased, the stroma was not conspicuous. A few endothelioid cells and giant cells and phagocytes were noted.

### DISCUSSION

From the foregoing summary of cases it seems possible to draw a number of interesting observations.

First of all, I wish to emphasize the close relationship between leukosarcoma, lymphosarcoma, and lymphatic leukæmia. Three leukosarcoma cases studied in The Johns Hopkins Department of Pathology, presented a blood picture of lymphatic leukæmia, general involvement of the lymphatic system, infiltration of the parenchymatous organs and bone marrow, associated with an invasive mediastinal tumor. One case beginning as a localized tumor of the chest developed a typical lymphatic leukæmia after X-ray treatment. The glands were enlarged all over the body, the liver and spleen descended below the costal margin. The subsequent findings at autopsy were similar to those in the cases mentioned above. It seems, then, that leukosarcoma combines the features of lymphosarcoma and lymphatic leukæmia and that a localized lymphosarcoma may under certain conditions become generalized and, with a blood picture of lymphatic leukæmia, may terminate as a leukosarcoma. Very important in this connection is the mode of spread of the lymphosarcoma group which, regardless of its primary site, extends in a characteristic manner first by local infiltration and later by the blood stream to parenchymatous organs, lymph glands, bone marrow, etc. At this stage only the negative blood findings differentiate the case from leukosarcoma and only the blood and the presence of

a local infiltrating mass differentiate it from lymphatic leukæmia. Finally, in lymphatic leukæmia one may see a similar mode of progression. The first cases, showing no increase in the number of blood lymphocytes, presented at autopsy hyperplastic lymphoid tissues with generalized infiltrations. Other cases, with a positive blood picture, showed more or less localized lymphoid involvement. The main group is quite typical but the last case developed, during the course of the leukæmia, large infiltrating masses in the inguinal regions. It appears, then, that in the leukæmia group some cases closely resemble certain types of lymphosarcoma, while others approach leukosarcoma.

Microscopically, the lymphocytic infiltrations of the organs in these diseases differs in quantity but not in quality. Distant lymph nodes appear the same in leukosarcoma as in lymphosarcoma and leukæmia. The parenchymatous organs and even the bone marrows are indistinguishable. Although the size and shape of the cell varies in the several cases it still retains its lymphoid character.

It appears not unlikely, then, that leukosarcoma, lymphosarcoma and lymphatic leukæmia are different manifestations of the same disease. In early life the primary focus may be in the small intestine or mediastinum. The disease then runs a rapid and fatal course spreading locally or generally (lymphosarcoma), occasionally to terminate with manifestations of lymphatic leukæmia (leukosarcoma). Later in life the focus may be anywhere and the course is more protracted. Extension, however, occurs in a similar manner. In many ways the disease is quite comparable with tuberculosis which in the young localizes in the chest or intestines, later to become spread more diffusely, and in adult life assumes many odd forms, attacking the kidney, uterus, skin, etc.

Next, I wish to say a word about the nature of this disease. From the preceding paragraph it may be seen that its local manifestations and mode of spread are not at all comparable to a malignant tumor with its metastases but simulate more closely the progress of an infectious disease. The site of origin is determined by an infiltrating mass of lymphoid cells not in themselves destructive but merely pushing aside normal tissue elements. Its mode of spread as a diffuse periportal infiltration, accumulation about the Malpighian bodies, scattered cells separating normal kidney tubules and glomeruli, homogeneous collections of cells in the bone marrow and other tissue, certainly does not find its parallel in the biology of any known tumor.

From unpublished observations by W. H. Lewis and L. T. Webster upon the activities of lymphocytes in tissue cultures (normal, tuberculous, lymphosarcomatous, Hodgkin's, and leukæmic lymph glands were cultured and the activity of the lymphocytes was studied), the following points may be valuable: (1) The lymphocyte in normal and pathological lymph nodes, observed in tissue cultures, is actively amœboid at body temperature and migrates, proceeding in a definite and characteristic manner for several days. (2) It probably responds to various chemical and bacterial substances. From the observation of many fixed sections from autopsies in which the lymphocytes, elongated and spindle-shaped, were similar to those in cultures and from experiments by Murphy it seems altogether probable that amœboid activity may take place on the part of the lymphocyte *in vivo*.

This lymphoid infiltration, then, variously designated as leukosarcoma, lymphosarcoma, and lymphatic leukæmia, may be best explained as a response to some chemotactic agent derived from a living organism. So long as this substance remains confined, the accumulation of lymphocytes is local but the presence of this substance in any part of the body, parenchymatous organs, glands, bone marrow, etc., produces in that area an infiltration of lymphocytes.

A minor point of some prognostic significance might be mentioned at this time. Several clinical cases where a lymph node had been removed for diagnosis showed microscopically evidence of amœboid activity on the part of the lymphocytes. All of these cases, 12, died within a few months.

Hodgkin's disease, a reticulo-endothelial cell proliferative process, in contrast to leukosarcoma, lymphosarcoma, and lymphatic leukæmia, which are lymphocytic proliferative processes, may be diagnosed microscopically and is probably a distinct entity.

Clinically, until a definite etiological agent has been discovered, these conditions will remain little more than diagnostic problems. From the study of 26 clinical cases of lymphosarcoma and 33 cases of Hodgkin's disease in which a lymph gland had been removed for examination, it seems that lymphosarcoma cannot always be diagnosed microscopically, and that in early cases it is unwise to give a certain prognosis. Hodgkin's disease, on the other hand, may be diagnosed from the microscopical examination of a single gland and a definite prognosis may be offered. Seven atypical cases in this series, however, the patients being alive and well from 2 to 11 years after examination, appear quite similar microscopically. The more or less homogeneous mass of lymphoid cells suggests some benign form of chronic lymphadenitis. Associated with these cases is frequently a so-called transient "infectious mononucleosis" in the blood characterized by an increase in the number of lymphoid cells.

## CONCLUSIONS

1. It seems probable that lymphosarcoma, lymphatic leukæmia, and leukosarcoma, are different manifestations of the same disease.

2. The term "lymphadenosis, leukæmic or aleukæmic" would express this idea and simplify the classification until a definite etiological agent is found.

3. This disease is not a neoplasm but a direct response on the part of lymphocytes to a chemotactic influence exerted by the disease-causing agent. The presence of this substance in any tissue or organ produces there a local accumulation of lymphoid cells.

4. Diagnosis and prognosis of this disease in its early stage is difficult from the microscopical examination of a single gland because of its resemblance to certain types of benign lymphadenitis.

5. Evidence of amœboid activity, on the part of the lymphocytes, is indicative of a rapid fatal course.

6. Hodgkin's disease, a distinct entity, may be diagnosed and accurately prognosed from the microscopical examination of a single gland.

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# SOME ADAPTIVE DIFFICULTIES FOUND IN SCHOOL CHILDREN[1]

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In the winter of 1916 and 1917 the Joint Committee on Education, of Chicago, invited a discussion in the interests of their public schools by representatives from the fields of biology, psychology, psychopathology and sociology. The contributions of these sciences were presented, respectively, by Herbert S. Jennings, John B. Watson and Adolf Meyer of The Johns Hopkins University and by William I. Thomas of the University of Chicago. The trend of these suggestions, derived independently from experience and research, lies in the direction of emphasis on the study of the individual child and his needs, rather than on the reference of the individual to a group.

In his paper entitled "Mental and Moral Health in a Constructive School Program" Dr. Meyer suggested that "a school physician with training in psychopathology attend regular conferences at which the management of problematic pupils is discussed," and arrange for the study with teachers and parents of any case recommended for special attention. The practical application of this idea was begun by the writer January, 1918, in Public School No. 76, which lies in the Locust Point District of Baltimore, previously reported on by Dr. C. M. Campbell (*Mental Hygiene*, Vol. 2, pp. 232-244). The 15 school months during which this study was made were interrupted by no less than three enforced school holidays of from two to eight weeks each, due to the influenza epidemic, plumbing tragedies and the burning of the main school building. These circumstances, together with the fact that only two days a week were devoted to this work, may comfort those who mourn that only 46 children were studied during the above period.

Requests for suggestions in regard to specific children were more than it was possible to compass. They came from the kindergarten to the eighth grade with a breadth of distribution exceeded only by the diversity of the individual complaint. Of the 46 children coming under observation 35 were reported as having difficulty in keeping up with their grade in one or more subjects. In each case where there was a question of retardation the Binet-Simon tests were applied. As a result 16 of the above mentioned 35 were found to have a mental retardation of from three to six years. The academic troubles of the remaining 19 retarded children were associated with, if not the disguised expression of, such faulty psycho-biological reactions as shyness, laziness, inattention, vicious tendencies, sensitiveness to criticism, day dreaming, hypochondriacal fears, etc. The 11 remaining from the total of 46 were referred for more overt adaptive difficulties of temper tantrums, sullenness, crying spells, twitching, indifference, excitability, poor co-ordination with the hands, quarrelsomeness, etc.

So familiar are the majority of such reactions in the world of every day that one hardly pauses to consider these facts. They seem to be the vague result of still vaguer causes. Faulty nutrition, inadequate exercise, the strain of defective light and ventilation, a poorly balanced school curriculum mustering under the banner of science, figure from time to time in drives of public health and educational controversy as abstract sponsors of these unhealthy manifestations of child life. But can one study such twists of behavior and mental attitudes in terms of abstract physiology, pedagogy or "child psychology"? What are the concrete facts about the shyness, twitching, and inattention of John and Henry? Each is as distinct in the array of data of his total function as in those of his special organs. He has had his own start in birth, early development, training and home influence, as well as in sleeping, eating and other factors of so-called personal hygiene. To understand his trouble in concentration, his temptations, his impulsive behavior, his lack of satisfaction in work and play, one must have a life record of the individual child in the stories of parent, teacher, physician and child himself. The facts of history, school report, habit data and personal examination were followed in each case by suggestions for modification, and as far as possible by careful subsequent notes. The results as tabulated in the original article are encouraging in spite of the handicap of overworked teachers and unsettled times. It is interesting to note that the children who responded with improvement from, and in many instances with complete disappearance of, the adaptive difficulty for which they were referred were found below the fifth grade.

In conclusion it should be stated that these studies were not undertaken for the purpose of obtaining statistical data on the neurotic child nor yet for purposes of adding to what has already been described in regard to the psychotic constitution.

[1] Abstract of a paper read at a meeting of the Federation for Child Study, New York City, January 28, 1920, and published in *Mental Hygiene*, Vol. 4, No. 2, April, 1920.

That some of the material presented can readily be correlated with these syndromes is as natural as that other case material falls into the group of mentally retarded children who are the subjects of most school surveys in the interests of mental hygiene. On the contrary, this work was taken up solely with a view of discovering some of the common adaptive difficulties of childhood, and of finding out whether one accustomed to studying sources of failure in individual human beings could be of help to parents and teachers who are baffled and perplexed by difficulties of development in their childish setting.

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## NEW PUBLICATIONS.

The following monograph is for sale by The Johns Hopkins Press, Baltimore, Md.:

**Relation of Tonsillar and Nasopharyngeal Infections to General and Systemic Disorders.** By S. J. Crowe, S. Shelton Watkins and Alma S. Rothholtz. 63 pages. Price, $1.25.

## ERRATA

Attention is called to a typographical error on page 365 of the October Bulletin, in the article entitled "The Coagulation Time of Citrated Plasma on Recalcination" by H. C. Gram. The second paragraph in the right hand column should read as follows:

The recalcination used is the result of experience which showed that the optimal recalcination always took place in the tubes containing 2, 3, 4 and 5 drops of a 1 per cent $CaCl_2, 6H_2O$. If instead of a 10 per cent solution a 3 per cent solution of citrate is used, the recalcination must be 1, 2, 3, and 4 drops. Cases of protracted coagulation time, where the optimal recalcination was 2 or 5 drops, were controlled afterwards with 1 or 6 drops, respectively, no errors being found.

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Attention is called to a typographical error on page 407 of the November Bulletin, in the article entitled "The Treatment of Neurosyphilis by the Intraspinal Route," by Albert Keidel and Joseph Earle Moore. Table II should read as follows:

| Diagnosis | No. of cases | Clinical result | | Serological result | |
|---|---|---|---|---|---|
| | | Good | Bad | Good | Bad |
| Tabes dorsalis | 6 | 4 | 2 | 1 | 4* |
| General paresis | 6 | 2 | 4 | 1 | 5 |
| Tabo-paresis | 2 | .. | 2 | .. | 2 |
| Cerebrospinal syphilis | 8 | 8 | .. | 5 | 3 |
| Asymptomatic neurosyphilis | 3 | 1 | 2 | .. | 3 |
| Total | 25 | 15 | 10 | 7 | 17 |

* One case, with negative serology at the start of treatment, remained unchanged.

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## JOHNS HOPKINS HOSPITAL BULLETIN

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